Intermolecular Nucleophilic Additions to Thermally-generated Benzynes and Mechanistic Studies

A DISSERTATION

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Juntian Zhang

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I dedicate this Thesis to

my family, and my girlfriend Jingchen Zhang

Abstract

ortho-Benzynes compose a highly versatile class of reactive intermediate in organic chemistry. They can be trapped *in situ* by a variety of nucleophile-electrophile pairs or enter into pericyclic reactions to generate multi-substituted arene moieties that can be further functionalized to different target molecules. Compare to traditionally generated benzynes (through elimination of arene derivatives), the thermally generated benzynes [through the hexadehydro-Diels–Alder (HDDA) reaction] provide both a synthetic approach to functionalized arene derivatives and unusual modes of reactivity.

In this Thesis, I will emphasize some of the more recent aspects of HDDA reactions as a tool for synthesizing multi-functionalized arene derivatives, along with divergent reaction pathways and mechanistic insight. Details of this Thesis include (i) the phenol-ene reaction to construct biaryl moieties (**Chapter 2**), (ii) reaction of HDDA-generated benzynes with *N*-heterocycles (**Chapter 3**), (iii) an atypical mode of "1,3-dipolar" cycloaddition reaction between benzynes and electron-deficient thioamides (**Chapter 4**), (iv) divergent reactivity by glycidol analogs: ring cleavage via pinacol-like rearrangements vs. oxirane fragmentations (**Chapter 5**), and (v) total synthesis of isohericerin using the HDDA reaction (**Chapter 6**).

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List of Abbreviations

°C	degree Celsius
Ac	acetyl
APCI	atmospheric pressure chemical ionization
Ar	aryl
AcOH	acetic acid
app.	apparent, in NMR spectroscopy
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad, in NMR spectroscopy
brsm	based on recovered starting material
Calc'd	calculated
Cy	cyclohexyl
d	doublet, in NMR spectroscopy
DA	Diels–Alder
DDA	dehydro-Diels–Alder
DDDA	didehydro-Diels–Alder
DCE	1,2-dichloroethane
DCM	dichloromethane
DFT	density functional theory
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
E	electrophile
EDCI	*N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride
Et	ethyl
Et_2O	diethyl ether

EtOAc	ethyl acetate
EtOH	ethanol
equiv.	equivalent
EWG	electron withdrawing group
g	gram(s)
GC-MS	gas chromatography-mass spectrometry
h	hour(s)
HDDA	hexadehydro-Diels–Alder
Hex	*normal*-hexyl or hexanes
HMBC	heteronuclear multiple bond correlation
HPLC	High Performance Liquid Chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	hertz
i-Pr	*iso*-propyl
i-PrOH	*iso*-propanol
IR	infrared
J	coupling constant, in NMR spectroscopy
k	rate constant
kcal	kilocalorie
LAD	lithium aluminum deuteride
LDA	lithium diisopropylamide
M	molar
m	*meta*-
m	multiplet, in NMR spectroscopy
Me	methyl

MeO	methoxy
MeOH	methanol
MHz	megahertz
mmol	millimole(s)
mp	melting point
MPLC	medium pressure liquid chromatography
MS	mass spectrometry
Ms	methanesulfonyl
n-Bu	*normal*-butyl
n-BuLi	*normal*-butyl lithium
NBS	*N*-bromosuccinimide
NEt_3	triethylamine
N-HAR	*N*-heteroaromatic compounds
n-Hep	*normal*-heptyl
NMR	nuclear magnetic resonance
n-Oct	*normal*-octyl
Nu	nucleophile
o	*ortho*
OTBS	*tert*-Butyldimethylsilyloxy
π	pi
p	*para*-
PG	protecting group
Ph	phenyl
PPh_3	triphenylphosphine
ppm	parts per million
q	quartet, in NMR spectroscopy

R	rectus, configuration
rt	room temperature
s	singlet, in NMR spectroscopy
S	sinister, configuration
sept	septet, in NMR spectroscopy
S_N2	substitution (nucleophilic, bimolecular)
t	triplet, in NMR spectroscopy
t-Bu	*tertiary*-butyl
$t_{1/2}$	half-life time
TBAF	tetrabutylammonium fluoride
TBS	tertiary-butyldimethyl
TCR	three-component coupling reaction
TDDA	tetradehydro-Diels–Alder
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
TS	transition state

Chapter 1. The Hexadehydro-Diels–Alder Reaction

1.1 Benzyne Chemistry: Structure, Reactivity, and Formation

ortho-Benzyne (**101**) is considered as one of the most versatile intermediates in chemistry. The existence of benzyne was first postulated in 1870 by Dreher and co-workers,[1] and the structure has been studied extensively by both experimental[2,3,4,5,6] and computational[7,8] methods. Previous studies suggested that among the major resonance contributors (i.e. **101**–**101c**, Figure 1), the strained alkyne **101** is the dominant resonance contributor, rather than cumulene **101a**, diradical **101b**, or zwitterion **101c**.

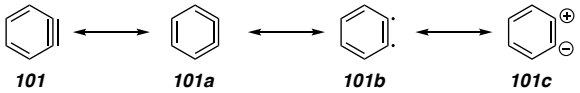

Figure 1. Major resonance contributors of simple benzyne.

Despite being highly reactive, benzyne has been known to "discriminate" what reacts with it.[9] In other words, benzyne reacts in a selective manner. The two most common modes of reactivities of benzyne are: 1. Pericyclic reactions (i.e., 1,3-dipolar

[1] Dreher, E.; Otto, R. Ueber Quecksilberdiphenyl. *Liebigs Ann. Chem.* **1870**, *154*, 93–130.
[2] Roberts, J. D.; Simmons, H. E., Jr; Carlsmith, L. A. Rearrangement in the Reaction of Chlorobenzene-1-C14 with Potassium Amide. *J. Am. Chem. Soc.* **1953**, *75*, 3290–3291.
[3] Leopold, D. G.; Miller, A.; Lineberger, W. C. Determination of the Singlet-Triplet Splitting and Electron Affinity of o-Benzyne by Negative Ion Photoelectron Spectroscopy. *J. Am. Chem. Soc.* **1986**, *108*, 1379–1384.
[4] Radziszewski, J. G.; Hess, B. A., Jr. Infrared Spectrum of o-Benzyne: Experiment and Theory. *J. Am. Chem. Soc.* **1992**, *114*, 52–57.
[5] Warmuth, R. *o*-Benzyne: Strained Alkyne or Cumulene? — NMR Characterization in a Molecular Container. *Angew. Chem. Int. Ed.* **1997**, *36*, 1347–1350.
[6] Wenthold, P. G.; Squires, R. R.; Lineberger, W. C. Ultraviolet Photoelectron Spectroscopy of the *o*-, *m*-, and *p*-Benzyne Negative Ions. Electron Affinities and Singlet-Triplet Splittings for *o*-, *m*-, and *p*-Benzyne. *J. Am. Chem. Soc.* **1998**, *120*, 5279–5290.
[7] Nash, J. J.; Squires, R. R. Theoretical Studies of *o*-, *m*-, and *p*-Benzyne Negative Ions. *J. Am. Chem. Soc.* **1996**, *118*, 11872–11883.
[8] Jiao, H.; Schleyer, P. V. R.; Warmuth, R.; Houk, K. N.; Beno, B. R. Theoretical Studies of the Structure, Aromaticity, and Magnetic Properties of *o*-Benzyne. *Angew. Chem. Int. Ed*. **1997**, *36*, 2761–2764.
[9] Mayr, H.; Ofial, A. R. The Reactivity–Selectivity Principle: An Imperishable Myth in Organic Chemistry. *Angew. Chem. Int. Ed.* **2006**, *45*, 1844–1854.

cycloaddition, Diels–Alder reaction, ene-reaction, etc.), and 2. Nucleophilic additions (with a Nu–E pair). If the benzyne is substituted, two regioisomeric products can potentially be formed, and the regioselectivity of the trapping event can be rationalized by the stereoelectronics of the benzyne itself. Computational studies to predict regioselectivity of an unsymmetrical benzyne were performed independently by Cramer[10] and Buszek, and by Garg and Houk[11].

Figure 2 shows the study of the distortion and regioselectivity of indolynes by Garg and co-workers.[11] They calculated the geometry of 4,5-indolyne **102**, 5,6-indolyne **103** and 6,7-indolyne **104**, and their distortion angles at the triple bond. Among the 3 indolyne derivatives, the 6,7-indolyne has the most distorted geometry, with the difference of the distortion angles of 18º. This is consistent with their experimental results, in which the reaction of indolyne **104** gave only 6-substituted indoles, while the other indolynes gave a mixture of two regioisomeric products. The regioselectivity can be rationalized by orbital theory: the more obtuse angle of the electrophilic site, the greater *p*-character, hence the better electrophilicity.

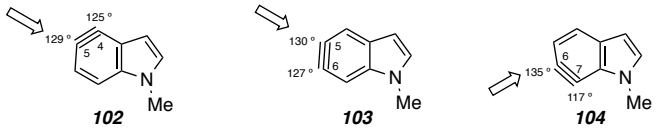

Figure 2. Study of the distortion of indolyne.

Benzynes have been generated by a number of traditional methods, most of which are through an elimination process of an *ortho*-disubstituted arene derivative.[12] Most of

[10] Garr, A. N.; Luo, D.; Brown, N.; Cramer, C. J.; Buszek, K. R.; VanderVelde, D. Experimental and Theoretical Investigations into the Unusual Regioselectivity of 4,5-, 5,6-, and 6,7-Indole Aryne Cycloadditions. *Org. Lett*. **2010**, *12*, 96–99.
[11] Cheong, P. H. Y.; Paton, R. S.; Bronner, S. M.; Im, G.-Y. J.; Garg, N. K.; Houk, K. N. Indolyne and Aryne Distortions and Nucleophilic Regioselectivites. *J. Am. Chem. Soc*. **2010**, *132*, 1267–1269.
[12] Tadross, P. M.; Stoltz, B. M. A Comprehensive History of Arynes in Natural Product Total Synthesis. *Chem. Rev*. **2012**, *112*, 3550–3577.

the methods of benzyne generation are depicted in Figure 3. As shown in the "wheel of benzyne generation", most of the methods involve a strong base (e.g., *n*-BuLi), or a fluoride source (e.g., TBAF, KF, and CsF), or under extreme conditions (e.g., excessive heating, and strong oxidant).

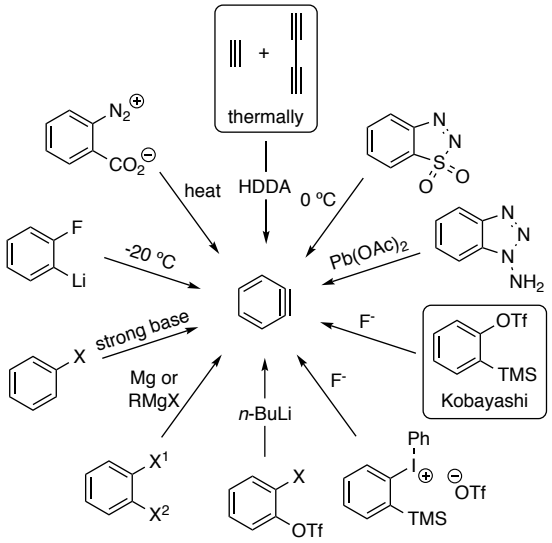

Figure 3. Traditional and thermal methods of benzyne generation.[12]

The Kobayashi[13] method of benzyne generation is by far the most commonly used method. Upon treating with a fluoride source (TBAF or alkali metal fluoride), the *ortho*-trimethylsilylaryltriflate readily undergoes a desilylation followed by an elimination of the triflate ion, resulting in the benzyne formation. This method is frequently implemented because it uses relatively mild conditions during benzyne generation, but the use of a fluoride source and the requirement of pre-installation of *ortho*-silyl and triflate group limits its usage. Compared to the Kobayashi method, the HDDA-generated (aka thermally-generated) benzyne does not require a base or a fluoride source, which could allow for a broader scope and new types of aryne chemistry to be revealed.

[13] Himeshima, Y.; Sonoda, T.; Kobayashi, H. Fluoride-induced 1,2-Elimination of o-Trimethylsilylphenyl Triflate to Benzyne Under Mild Conditions. *Chem. Lett.* **1983**, *8*, 1211–1214.

1.2 Early Studies of the Hexadehydro-Diels–Alder (HDDA) Reaction

The Diels–Alder reaction[14] has been one of the most well-studied pericyclic reactions in the past century. In the prototypical Diels–Alder reaction, a butadiene (diene) reacts with an ethylene (dienophile) to give cyclohexene as the product. One type of the variants of the Diels–Alder reactions is referred to as the "dehydro-Diels–Alder" (DDA) reactions (Figure 4).[15] These types of variants can be categorized by their degree of unsaturation compared to the parent Diels–Alder reaction [namely, didehydro-Diels–Alder (DDDA), tetradehydro-Diels–Alder (TDDA), and hexadehydro-Diels–Alder (HDDA)], by removal of 2, 4, or 6 hydrogen atoms from the reactants, respectively.[16]

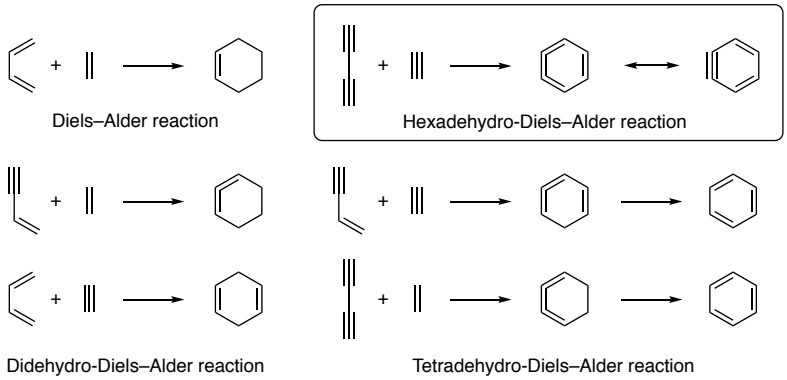

Figure 4. Prototypical variants of the Dehydro-Diels–Alder reactions.

Despite that numerous results have been published on DDDA and TDDA reactions,[15] it was not until 1997 that the first two reports of a HDDA reaction came into literature. Enlightened by the previous discovery of the Bergman cyclization,[17] Johnson and co-workers accomplished the first example of the HDDA reaction, in which they performed a flash vacuum pyrolysis of 1,3,8-nonatriyne (**105**) to generate a mixture of

[14] Diels, O.; Alder, K. Syntheses in the hydroaromatic series. *Justus Liebigs Ann. Chem*. **1928**, *460*, 98–122.
[15] Wessig, P.; Müller, G. The Dehydro-Diels−Alder Reaction. *Chem. Rev*. **2008**, *108*, 2051–2063.
[16] Ajaz, A.; Bradley, A. Z.; Burrell, R. C.; Li, W. H. H.; Daoust, K. J.; Bovee, L. B.; DiRico, K. J.; Johnson, R. P. Concerted vs Stepwise Mechanisms in Dehydro-Diels–Alder Reactions. *J. Org. Chem.* **2011**, *76*, 9320–9328.
[17] Bergman, R. G. Reactive 1,4-dehydroaromatics. *Acc. Chem. Res*. **1973**, *6*, 25–31.

indane (**107**) and indene (**108**) and some "soot", via a hypothetical indanyne (**106**, Figure 5, panel a) intermediate.[18] Presumably the indane formation was through a dihydrogen atom transfer, and further oxidation of indane (**107**) to generate indene (**108**). In the same year, Ueda and co-workers independently reported that the synthesis of the fluorenol derivative **112** can be achieved by a cycloisomerization reaction of the tetrayne **109**.[19] Ueda proposed that the reaction went through a radical intermediate **110**, which subsequently ejected a diphenylmethyl radical to give phenyl radical **111**, followed by a termination to give fluorenol **112**.

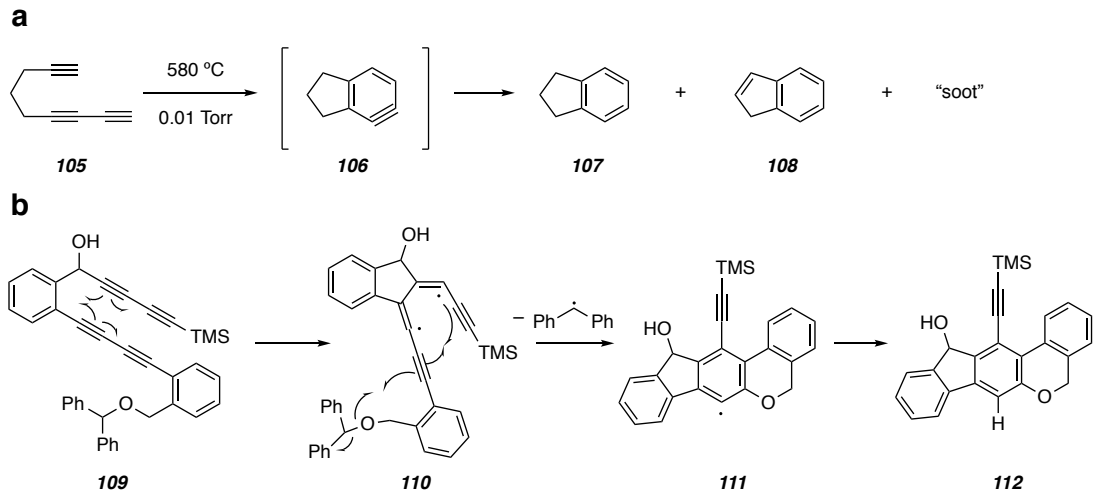

Figure 5. First reports of the HDDA reaction by (a) Johnson, and (b) Ueda.

Although the initial diradical formation proposed by Ueda is not fallacious, the overall reaction mechanism was proposed through radical pathways. Being biased and possibly then limited with their interpretation, Ueda *et al.* did not proceed to investigate more of this unique transformation to a broader scope, rather they focused on fluorenol

[18] Bradley, A. Z.; Johnson, R. P. Thermolysis of 1,3,8-Nonatriyne: Evidence for Intramolecular [2 + 4] Cycloaromatization to a Benzyne Intermediate. *J. Am. Chem. Soc.* **1997**, *119*, 9917–9918.
[19] Miyawaki, K.; Suzuki, R.; Kawano, T.; Ueda, I. Cycloaromatization of a non-conjugated polyenyne system: Synthesis of 5H-benzo[d]fluoreno[3,2-b]pyrans via diradicals generated from 1-[2-{4-(2-alkoxymethylphenyl)butan-1,3-diynyl}]phenylpentan-2,4-diyn-1-ols and trapping evidence for the 1,2-didehydrobenzene diradical. *Tetrahedron Lett.* **1997**, *38*, 3943-3946.

tetrayne precursors and a limited number of traps.[20,21,22,23,24,25,26,27] Those reports did not raise much attention to a broader audience.

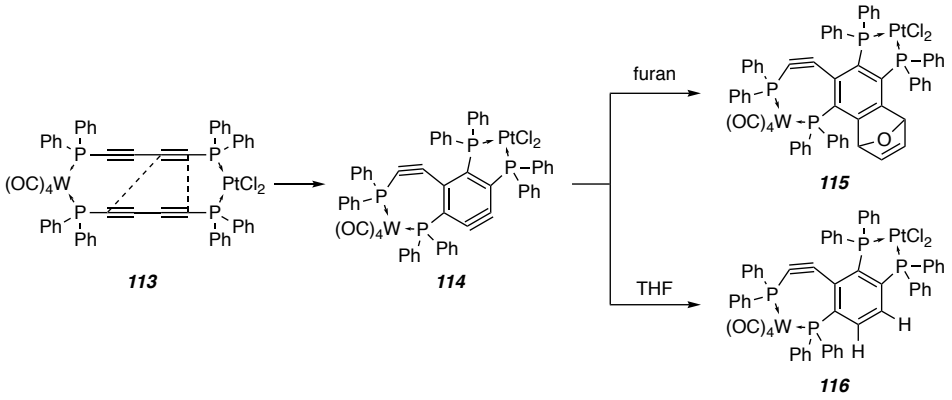

Figure 6. Transition metal-assisted HDDA cycloisomerization.

There has also been one (and the only) report of a transition metal-templated HDDA cycloisomerization prior to 2012. Sterenberg *et al.* reported that a transition metal-tethered polyyne precursor **113** can undergo HDDA cyclization at room temperature to give the benzyne intermediate **114** (Figure 6), which was then trapped by furan (via

[20] Miyawaki, K.; Kawano, T.; Ueda, I. Multiple cycloaromatization of novel aromatic enediynes bearing a triggering device on the terminal acetylene carbon. *Tetrahedron Lett.* **1998**, *39*, 6923–6926.
[21] Ueda, I.; Sakurai, Y.; Kawano, T.; Wada, Y.; Futai, M. An unprecedented arylcarbene formation in thermal reaction of non-conjugated aromatic enetetraynes and DNA strand cleavage. *Tetrahedron Lett.* **1999**, *40*, 319–322.
[22] Miyawaki, K.; Kawano, T.; Ueda, I. Domino thermal radical cycloaromatization of non-conjugated aromatic hexa- and heptaynes: Synthesis of fluoranthene and benzo[a]rubicene skeletons. *Tetrahedron Lett.* **2000**, *41*, 1447–1451.
[23] Kawano, T.; Inai, H.; Miyawaki, K.; Ueda, I. Synthesis of indenothiophenone derivatives by cycloaromatization of non-conjugated thienyl tetraynes. *Tetrahedron Lett*. **2005**, *46*, 1233–1236.
[24] Kawano, T.; Inai, H.; Miyawaki, K.; Ueda, I. Effect of water molecules on the cycloaromatization of non-conjugated aromatic tetraynes. *Bull. Chem. Soc. Jpn*. **2006**, *79*, 944–949.
[25] Kawano, T.; Suehiro, M.; Ueda, I. Synthesis and inclusion properties of 6,6′-Bi(benzo[b]fluoren-5-ol) derivative by cycloaromatization. *Chem. Lett.* **2006**, *35*, 58–59.
[26] Kimura, H.; Torikai, K.; Miyawaki, K.; Ueda, I. Scope of the thermal cyclization of nonconjugated ene–yne–nitrile system: A facile synthesis of cyanofluorenol derivatives. *Chem. Lett*. **2008**, *37*, 662–663.
[27] Torikai, K.; Otsuka, Y.; Nishimura, M.; Sumida, M.; Kawai, T.; Sekiguchi, K.; Ueda, I. Synthesis and DNA cleaving activity of water-soluble non-conjugated thienyl tetraynes. *Bioorg. Med. Chem.* **2008**, *16*, 5441–5451.

[4+2]-cycloaddition) or tetrahydrofuran (via dihydrogen atom transfer).[28] The metals on the tether of the polyyne precursor **113** were shown to be critical, and are not coordinating directly to the diyne. This report demonstrated that benzyne can be spontaneously generated by tethered diynes, which further sets the foundation to future discoveries.

1.3 Serendipitous "Discovery" of the HDDA Reaction

In a totally unrelated study of an 9-membered enediyne in late 2011, Dr. Beeru Baire in our lab attempted to prepare ynone **118** from alcohol **117** using the standard MnO_2 oxidation procedure. After 5 hours stirring at ambient temperature, Dr. Baire isolated a product in 53% yield, and characterization by ^1H NMR experiments showed that it was not the desired ynone **118**. By a series of characterization experiments, he was able to elucidate the structure and found that the product was, instead, the indenone **120**.[29] Hoye and co-workers proposed that the product was formed through a [4+2]-cyclization to generate the benzyne **119a**, followed by a retro-Brook[30] rearrangement to yield the stable tricyclic indanone **120**.

As shown in Figure 8, Hoye *et al.* demonstrated that many triynes (**121a–c**, **e–f**) and tetrayne **121d** are capable of generating benzyne under purely thermal conditions. Various tethers, including but not limited to, cyclohexene (Figure 8a, **121a**), ether (Figure 8a, **121b**), ynamide (Figure 8a, **121c**), malonate (Figure 8a, **121d**), and fluorenone (Figure 8a, **121e–f**), have been studied. The cyclization temperature and half-life are

[28] Tsui, J. A.; Sterenberg, B. T. A Metal-Templated 4 + 2 Cycloaddition Reaction of an Alkyne and a Diyne To Form a 1,2-Aryne. *Organometallics* **2009**, *28*, 4906–4908.
[29] Hoye, T. R.; Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P. The hexadehydro-Diels–Alder reaction. *Nature* **2012**, *490*, 208–212.
[30] Hoye, T. R.; Baire, B.; Wang, T. Tactics for probing aryne reactivity: mechanistic studies of silicon-oxygen bond cleavage during the trapping of (HDDA-generated) benzynes by silyl ethers. *Chem. Sci.* **2014**, *5*, 545–550.

determined by the tether[31], as well as the substituent on the 4π or 2π components[32]. However, it is noteworthy that most of the tethers consist of three atoms. Other membered tethers have been studied and were either forming too strained ring system (2-membered tether, to give benzocyclobutane derivatives), or the 4π and 2π components being too far apart, making the cyclization less feasible at mild temperature (4-membered tether, to give benzocyclohexane derivatives). To date, there is only one 5-membered tether reported[29], and it cyclizes under highly elevated temperatures (> 200 ºC).

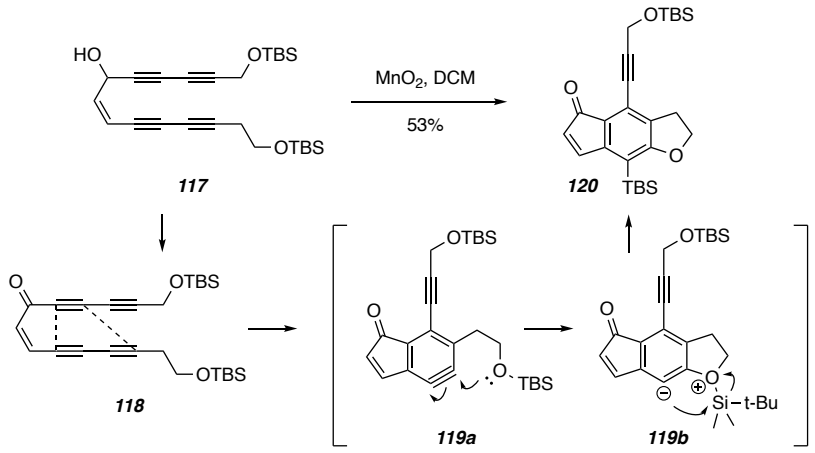

Figure 7. Serendipitous discovery of the HDDA reaction cascade in Hoye lab.

Trapping of the HDDA-derived benzyne can occur both intra- (Figure 8a) and intermolecularly (Figure 8b). Compared to traditionally-generated benzynes, the thermally generated benzyne can undergo trapping reactions in similar fashion, namely, either by a Nu–E pair to give products **122a–d, g, k**, or via pericyclic reactions to give products **122e–f, h–j**. In addition, since the benzyne is thermally generated without the presence of additives, it can enable completely new reactivities that would not occur in

[31] Woods, B. P.; Baire, B.; Hoye, T. R. Rates of hexadehydro-Diels−Alder (HDDA) cyclizations: impact of the linker structure. *Org. Lett*. **2014**, *16*, 4578−4581.
[32] Wang, T.; Niu, D.; Hoye, T. R. The hexadehydro-Diels–Alder cycloisomerization reaction proceeds by a stepwise mechanism. *J. Am. Chem. Soc*. **2016**, *138*, 7832–7835.

the traditional fashion. We will discuss those atypical modes of reactivities in later chapters.

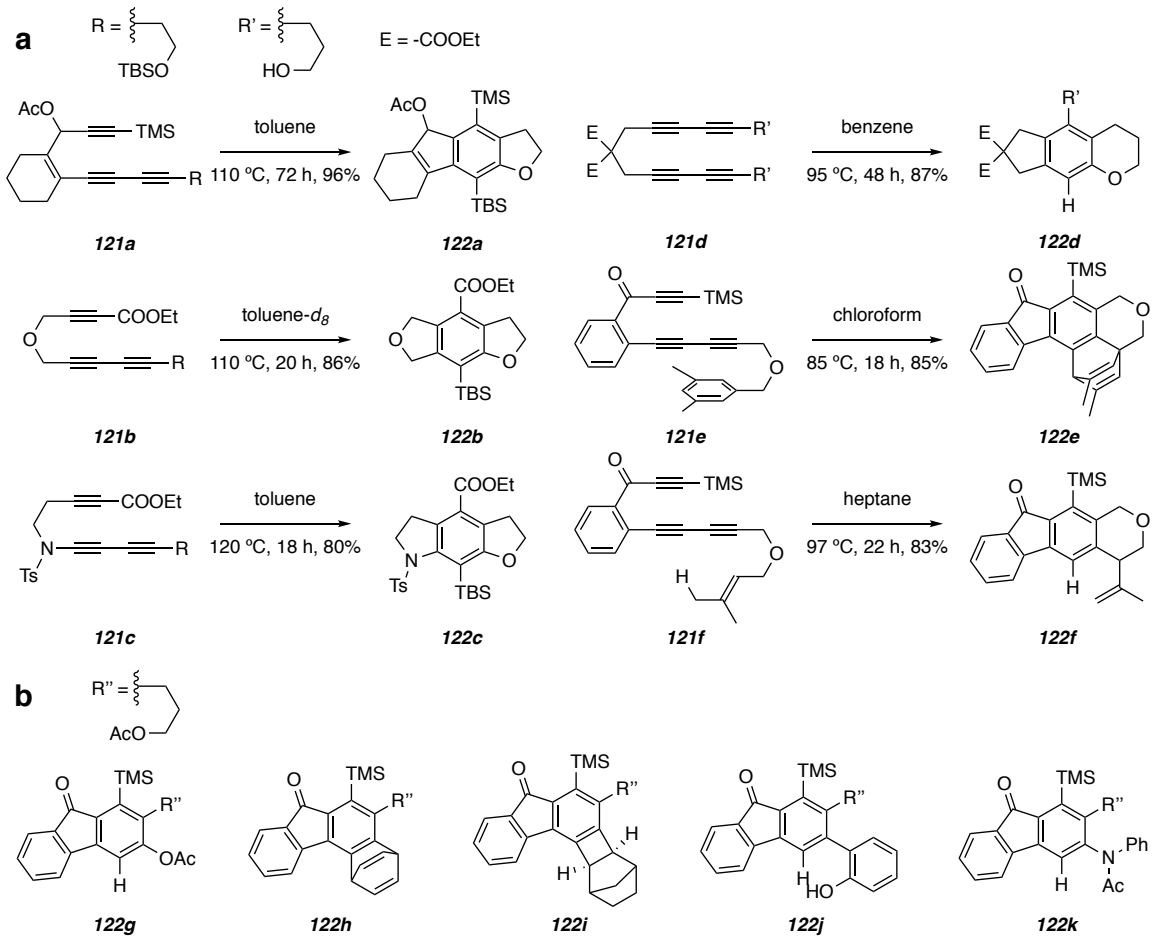

Figure 8. (a) Intra- and (b) intermolecular trapping of the HDDA reaction.

1.4 Mechanistic Study of the HDDA-derived Benzyne Formation

In 2011, Johnson and co-workers performed DFT calculations of the energetics of the DDA reactions.[16] They found that compared to the parent Diels–Alder reaction, in which the product cyclohexene is -36 kcal•mol^{-1},[33] the DDA reactions in general are less

[33] Goldstein, E.; Beno, B.; Houk, K. N. Density Functional Theory Prediction of the Relative Energies and Isotope Effects for the Concerted and Stepwise Mechanisms of the Diels−Alder Reaction of Butadiene and Ethylene. *J. Am. Chem. Soc*. **1996**, *118*, 6036–6043.

exothermic (DDDA: -14.1, TDDA: -2.7 and -25.8 kcal•mol^{-1}), due to the fact that the products are strained allenes or cumulenes (Figure 9, panel a–c), which further react *in situ* and are typically not isolated. However, the exception is the HDDA reaction (Figure 9, panel d), in which the product (benzyne) is -51 kcal•mol^{-1} downhill compared to the starting diyne and diynophile. This indicated that the HDDA-derived benzyne was formed in a highly exothermic fashion!

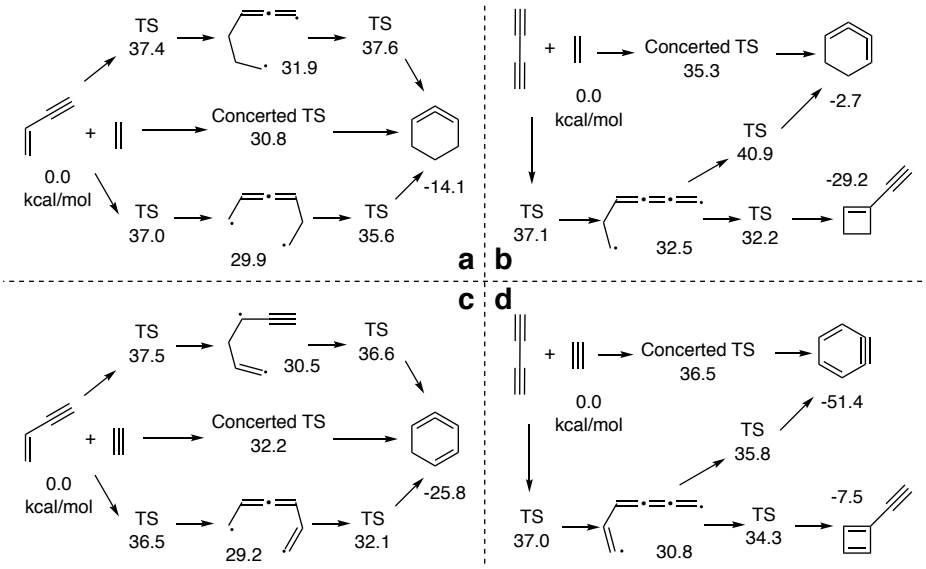

Figure 9. Computation results of DDA reactions.

In addition to the overall exothermicity of the HDDA reaction, Johnson also proposed two possible cyclization pathways of the prototypical HDDA cyclization. The stepwise pathway forms a vinyl cumulenyl diradical species, which further bifurcates to simple benzyne and ethynylcyclobutadiene. Comparing the activation energy of the concerted (36.5 kcal•mol^{-1}) vs. stepwise (37.0 kcal•mol^{-1}), there is a small preference for

the concerted mechanism. Further studies by Houk[34], Johnson[35] and Trolez[36] also suggested that the HDDA reaction mechanism are dependent on the substituent on the polyyne precursors, but with a more radical stabilizing group (e.g., alkynyl), the stepwise pathway is more favored.

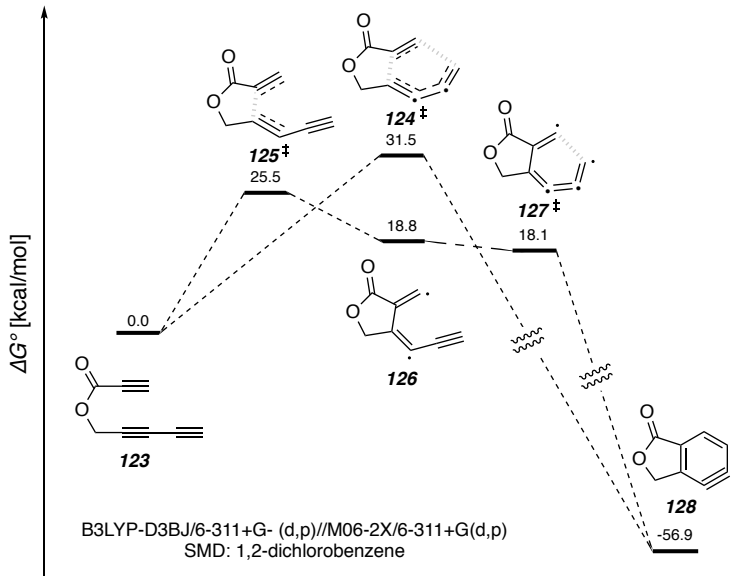

Figure 10. Mechanism of an HDDA cyclization reported by the Hoye group.

Our group (in collaboration with Cramer and Kuwata) also reported a computational study on HDDA cyclization mechanism.[37,38] They found out that the rate determining step for the stepwise transition state (TS) **125** is 6 kcal•mol^{-1} lower than the concerted TS **124**. This is a remarkable difference favoring the stepwise pathway.

[34] Liang, Y.; Hong, X.; Yu, P.; Houk, K. N. Why alkynyl substituents dramatically accelerate hexadehydro-Diels–Alder (HDDA) reactions: stepwise mechanisms of HDDA cycloadditions. *Org. Lett*. **2014**, *16*, 5702−5705.
[35] Skraba-Joiner, S. L.; Johnson, R. P.; Agarwal, J. Dehydropericyclic reactions: symmetry-controlled routes to strained reactive intermediates. *J. Org. Chem*. **2015**, *80*, 11779–11787.
[36] Kerisit, N.; Toupet, L.; Larini, P.; Perrin, L.; Guillemin, J.-C.; Trolez, Y. Straightforward synthesis of 5-bromopenta-2,4-diynenitrile and its reactivity towards terminal alkynes: a direct access to diene and benzofulvene scaffolds. *Chem.-Eur. J*. **2015**, *21*, 6042−6047.
[37] Marell, D. J.; Furan, L. R.; Woods, B. P.; Lei, X.; Bendelsmith, A. J.; Cramer, C.J.; Hoye, T. R.; Kuwata, K. T. Mechanism of the intramolecular hexadehydro-Diels–Alder reaction. *J. Org. Chem*. **2015**, *80*, 11744–11754.
[38] SMD(o-dichlorobenzene)/B3LYP-D3BJ/6-311+G-(d,p)//M06-2X/6-311+G(d,p).

Moreover, the second step via **127** of the stepwise pathway is -0.7 kcal•mol^{-1} compared to the diradical intermediate **126**, making the whole reaction pathway rather "concerted, but highly asynchronized". This is consistent with our observation (no radical character observed in any of the HDDA trapping step), and the mechanism was also experimentally[32] studied by our group.

1.5 New Reactivities and Applications of the HDDA Reaction

Due to the fact that the HDDA-derived benzyne is generated thermally, without any base or other additives, it can uncover new modes of reactivities that are unprecedented. In this section, I will focus on the studies that were influential to my research in intermolecular trapping reaction by oxygen (**Chapter 2** and **5**), nitrogen (**Chapter 3**) and sulfur (**Chapter 4**) nucleophiles, as well as a total synthesis utilizing the HDDA reaction to build the key ring (**Chapter 6**).[39]

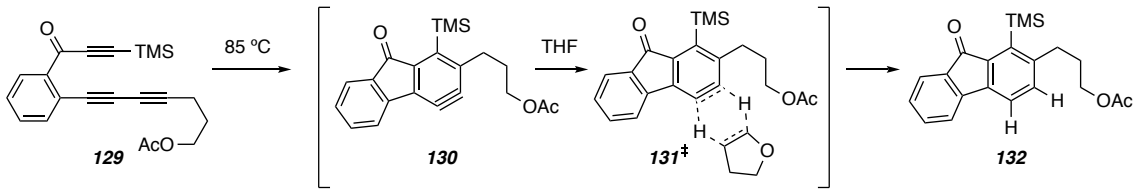

Figure 11. Alkane desaturation by concerted dihydrogen atom transfer to benzyne.

One early example was reported by Niu *et al.* in 2013 that HDDA-derived benzyne can be reduced by a dihydrogen transfer of a variety of cyclic alkanes (Figure 11). [40] When triyne precursor **129** was heated in THF at 85 ºC, benzyne **130** was formed and then underwent a dihydrogen atom transfer to generate arene **132**. If a 1:1 mixture of THF and THF-d_8 was used as solvent, only dihydrogenated or dideuterated arene was

[39] For a comprehensive review on the recent advance of the HDDA chemistry, please see: Diamond, O. J.; Marder, T. B. Methodology and applications of the hexadehydro-Diels–Alder (HDDA) reaction. *Org. Chem. Front.* **2017**, *4*, 891−910.

[40] Niu, D.; Willoughby, P. H.; Woods, B. P.; Baire, B.; Hoye, T. R. Alkane desaturation by concerted double hydrogen atom transfer to benzyne. *Nature* **2013**, *501*, 531–534.

observed, suggesting that this reaction occurs via a concerted, bimolecular transition state **131**. A variety of cyclic alkanes (e.g., cyclooctane, and norbornane) can also serve as dihydrogen donor to achieve this metal-free, C–H activation event.

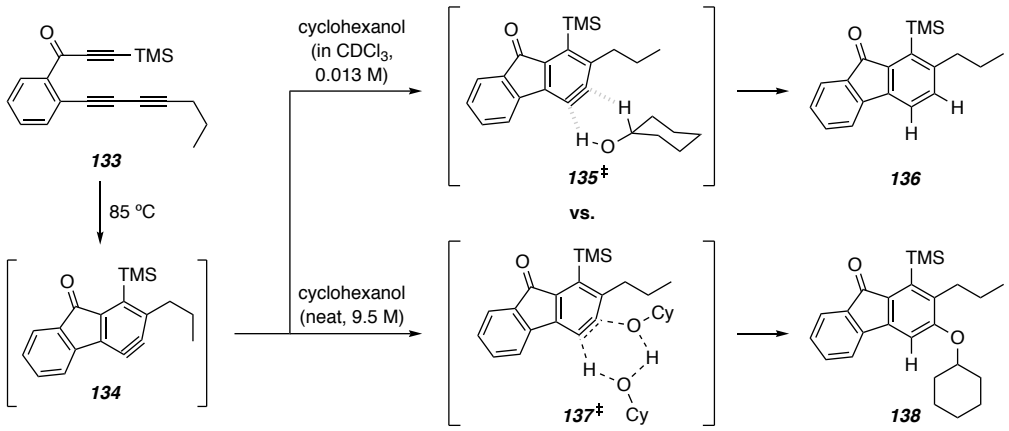

Figure 12. Competition between –OH addition and dihydrogen atom transfer on a HDDA-derived benzyne.

Primary or secondary alcohols are also found to reduce thermally-generated benzyne through dihydrogen atom transfer (Figure 12). In 2014, Willoughby *et al.* reported the mechanism of alcohol trapping of thermally-generated benzynes.[41] When triyne **133** was heated in the presence of cyclohexanol, divergent reaction pathways were observed depending on the concentration of cyclohexanol. If the concentration of the alcohol is dilute, the benzyne **134** is more prone to be reduced by the secondary alcohol to give saturated arene **136** with a small amount of aryl ether **138** (**136**:**138** = 17:1), and with cyclohexanone as the byproduct. If the benzyne is heated in neat cyclohexanol, instead, ether **138** was isolated in 80% yield with 12:1 ratio of arene **136** as minor product. Computation suggested that the dihydrogen transfer occurs via a similar 6-membered transition state (cf. **135**), while the OH addition was achieved via a 6-

[41] Willoughby, P. H.; Niu, D.; Wang, T.; Haj. M. K.; Cramer, C. J.; Hoye, T. R. Mechanism of the reactions of alcohols with o-benzynes. *J. Am. Chem. Soc*. **2014**, *136*, 13657–13665.

membered transition state (cf. **137**) with the alcohol dimer. Subsequent kinetic study verified that the oxidation of alcohol was first order, whereas the OH addition was second order with respect to cyclohexanol.

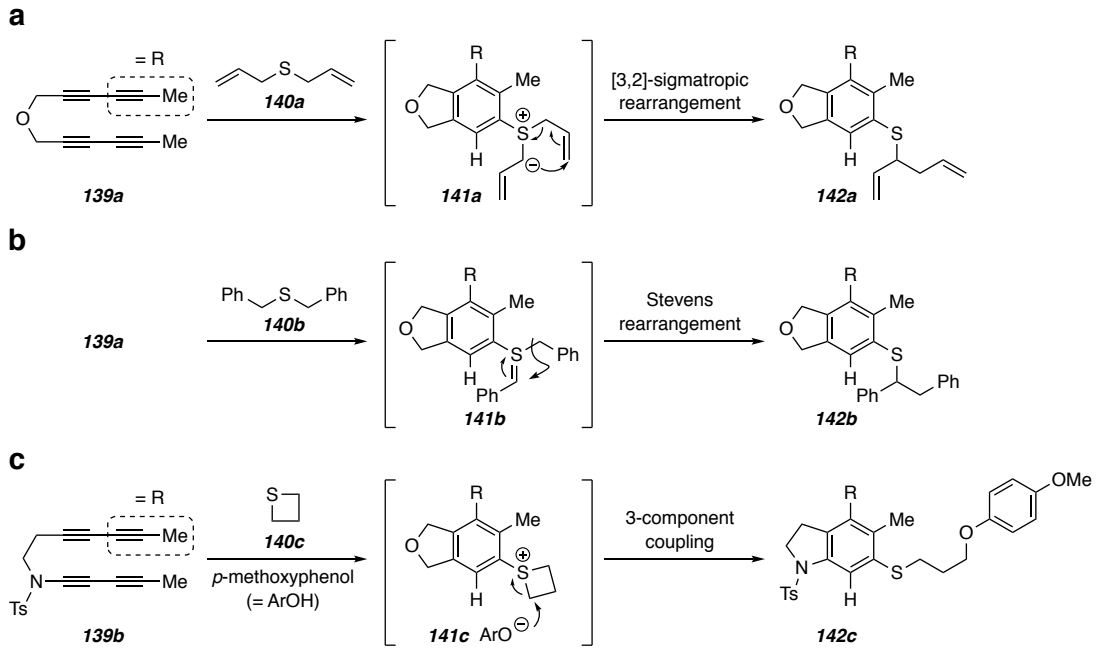

Figure 13. Various types of reactions including (a) [3,2]-sigmatropic rearrangement, (b) Stevens rearrangement, and (c) 3-component coupling observed in trapping events between HDDA-generated benzynes and sulfides.

Apart from oxygen nucleophiles like alcohols and ethers, our group has also studied sulfide trapping of thermally-generated benzynes. Dr. Junhua Chen and his undergraduate mentee Vignesh Palani have shown various types of reactions that sulfide can undergo when encountering an HDDA-generated benzyne.[42] If diallyl sulfide (**140a**) is used as the trapping agent, the sulfur atom of the disulfide will attack the benzyne, followed by a proton transfer to give sulfonium ylide **141a** from which a subsequent [3,2]-sigmatropic rearrangement occur to give thioether **142a** (Figure 13, panel a). Stevens rearrangement

[42] Chen, J.; Palani, V.; Hoye, T. R. Reactions of HDDA-Derived Benzynes with Sulfides: Mechanism, Modes, and Three-Component Reactions. *J. Am. Chem. Soc*. **2016**, *138*, 4318–4321.

will arise from ylide **141b** to produce thioether **142b** in 25% yield. When a third, protic component is present during the trapping event of a cyclic thioether **140c**, a 1:1:1 adduct **142c** will be isolated in 65% yield, via zwitterion **141c** and a subsequent ring-opening of the strained thietane ring. The divergent reactivity of sulfur ylide set the foundation for our study in ammonium ylides in **Chapter 4**.

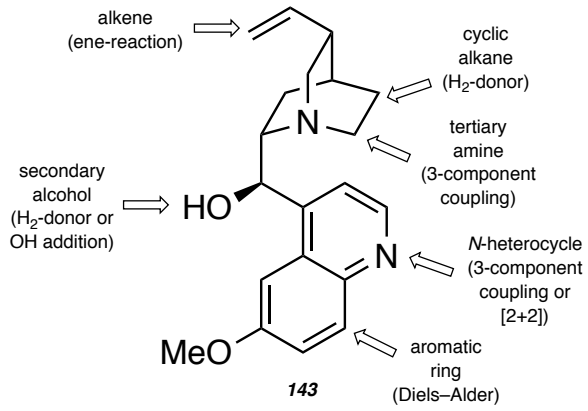

Figure 14. Multifunctionality of quinine when react with thermally-generated benzynes.

Natural products are structurally complex and multifunctional. Since benzyne can almost react with everything it encounters, the multiple reactive sites on a natural product will allow for competition of multiple products formation. For instance, the natural product quinine (**143**, Figure 14) contains a mono-substituted alkene moiety, which allows for intermolecular Alder-ene type reactions.[43,44] It also has cyclic alkane[40] and a secondary alcohol[41] functional groups, enabling H_2-transfer and OH addition. Moreover, the quinuclidine moiety is a tertiary amine which can attack the benzyne and then ensue 3-component coupling reaction.[45,46]. Quinine is also a *N*-heterocycle, and the reactivity

[43] Karmakar, R.; Mamidipalli, P.; Yun, S. Y.; Lee, D. Alder-Ene Reactions of Arynes. *Org. Lett*. **2013**, *15*, 1938−1941.
[44] Gupta, S.; Xie, P.; Xia, Y.; Lee, D. Reactivity of arynes toward functionalized alkenes: intermolecular Alder-ene vs. addition reactions. *Org. Chem. Front*. **2018**, *5*, 2208–2213.
[45] Ross, S. P.; Baire, B.; Hoye, T. R. Mechanistic Duality in Tertiary Amine Additions to Thermally Generated Hexadehydro-Diels–Alder Benzynes. *Org. Lett.* **2017**, *19*, 5705–5708.
[46] Ross, S. P.; Hoye, T. R. Multiheterocyclic Motifs via Three-Component Reactions of Benzynes, Cyclic

towards HDDA-benzyne will be discussed in **Chapter 3**.[47] Finally, the electron-rich aromatic ring on the quinoline might undergo Diels–Alder reaction with the benzyne.[48,49]

Dr. Sean Ross in our group was interested in how this molecule bearing multifunctional groups will interact with benzyne. He heated the tetrayne **144** with 1.5 equiv. of quinine (**143**) in benzene, and isolated two products with very similar NMR spectra. After a series of NMR experiments and analyses, the structure was identified as epoxide and piperidine ring-containing product **146a** (with around same amount of regioisomer[50] **146b**, Figure 15).[51] This presumably arose from a nucleophilic attack by the quinuclidine nitrogen atom, followed by an intramolecular proton transfer to give the alkoxy ammonium zwitterion, and successive bicyclic ring cleavage to produce the (*R,R*)-epoxide **146a/b**. This is another example showing the thermally-generated benzyne has remarkable levels of site selectivity, and is "discriminating".[9]

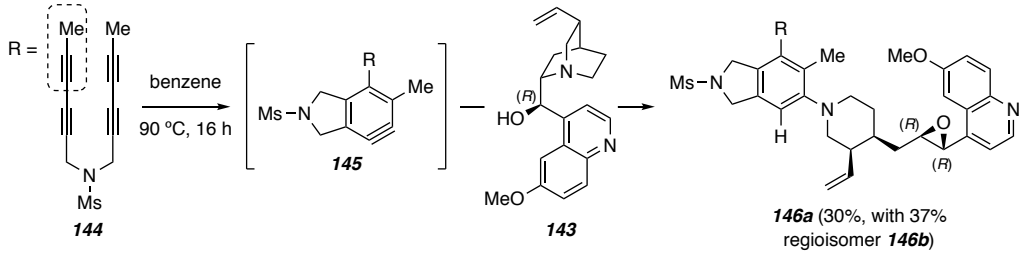

Figure 15. Reaction of HDDA-generated benzyne with quinine.

Amines, and Protic Nucleophiles. *Org. Lett.* **2018**, *20*, 100–103.

[47] Arora, S.; Zhang, J.; Pogula, V.; Hoye, T. R. Reactions of (HDDA-generated) benzynes with six-membered *N*–heteroaromatics: Pathway and product diversity. *Manuscript submitted to Chem. Sci.*

[48] Niu, D.; Wang, T.; Woods, B. P.; Hoye, T. R. Dichlorination of (hexadehydro-Diels–Alder generated) benzynes and a protocol for interrogating the kinetic order of bimolecular aryne trapping reactions. *Org. Lett.* **2014**, *16*, 254–257.

[49] Pogula, V. D.; Wang, T.; Hoye, T. R. Intramolecular [4 + 2] trapping of a hexadehydro-Diels–Alder (HDDA) benzyne by tethered arenes. *Org. Lett*. **2015**, *17*, 856–859.

[50] This symmetrical benzyne **145** almost has no distortion so that it gives almost 1:1 regioisomers in most of the cases.

[51] Ross, S. P.; Hoye, T. R. Reactions of hexadehydro-Diels–Alder benzynes with structurally complex multifunctional natural products. *Nature Chem.* **2017**, *9*, 523–530.

Besides mechanistic studies in trapping events, thermally-generated benzynes have also been demonstrated its synthetic utility in total syntheses, allowing multifunctionalized arene rings be constructed in a single step.[12,52] There are only a few known total syntheses utilizing HDDA reaction reported in the literature. In 2016, Dr. Tao Wang in our group reported total syntheses of alkaloids of the *Murraya koenigii* family exploiting the carbazolyne chemistry.[53] For example, natural product koenidine can be synthesized in 7 steps from commercially available aniline derivative **147** (Figure 16). The first alkyne moiety was installed by a Sonogashira cross coupling reaction of bromoarene **147** and ethynyltrimethylsilane, then a toluenesulfonyl (Ts-) group was

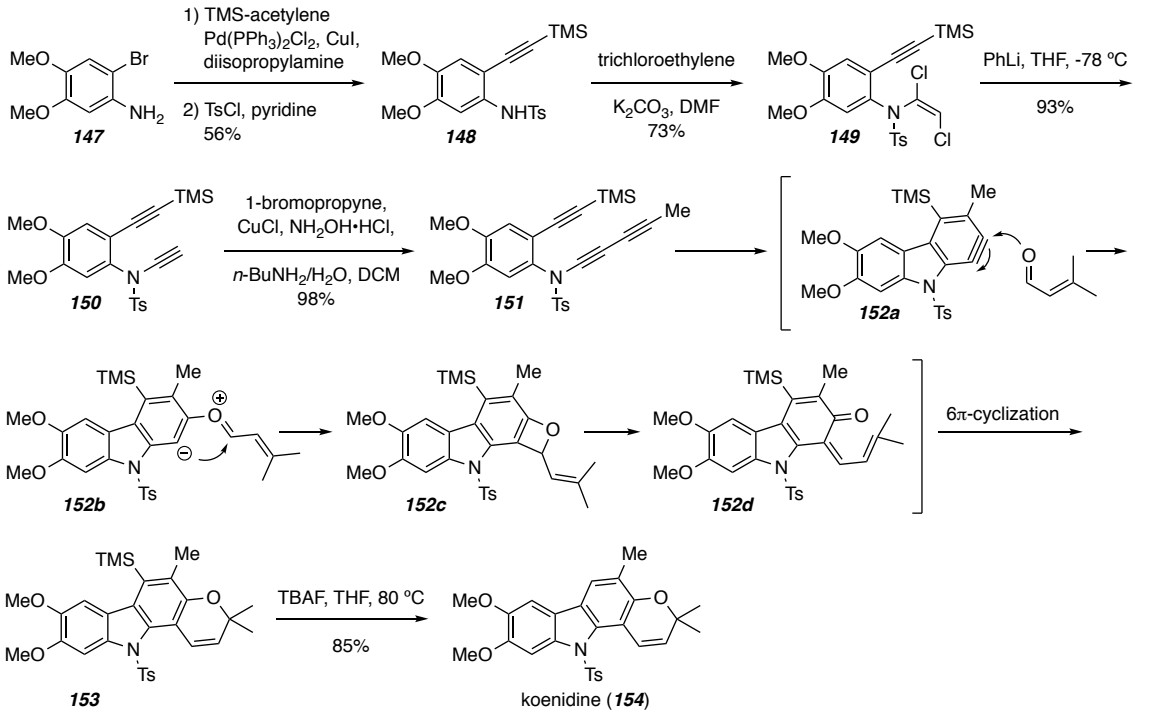

Figure 16. Total synthesis of koenidine, an alkaloid of the *Murraya koenigii* family.

[52] Gampe, C. M.; Carreira, E. M. Arynes and cyclohexyne in natural product synthesis. *Angew. Chem. Int. Ed.* **2012**, *51*, 3766–3778.
[53] Wang, T.; Hoye, T. R. Hexadehydro-Diels−Alder (HDDA)-enabled carbazolyne chemistry: Single step, de novo construction of the pyranocarbazole core of alkaloids of the Murraya koenigii (curry tree) family. *J. Am. Chem. Soc.* **2016**, *138*, 13870–13873.

installed on the aniline, followed by the preparation of dichloroenamine **149**. Next, the ynamide **150** was formed in good yield via an elimination reaction, and was subsequently subjected to copper-catalyzed Cadiot–Chodkiewicz cross coupling with bromopropyne to give the triyne precursor **151**.

The key HDDA reaction cascade proceeded through a nucleophilic attack on the aryne **152a** by the oxygen atom on dimethylacrolein, and a ring closure to provide the formal [2+2]-adduct **152c**. A electrocyclic ring opening of the benzoxetene **152c** gave the *ortho*-quinone methide **152d** under thermal conditions, and a 6-π electrocyclization reaction then occurred to produce carbazole **153**. Removal of the silyl protecting group gave koenidine (**154**) in 85% yield. The 7-step total synthesis was accomplished in overall 32% yield.

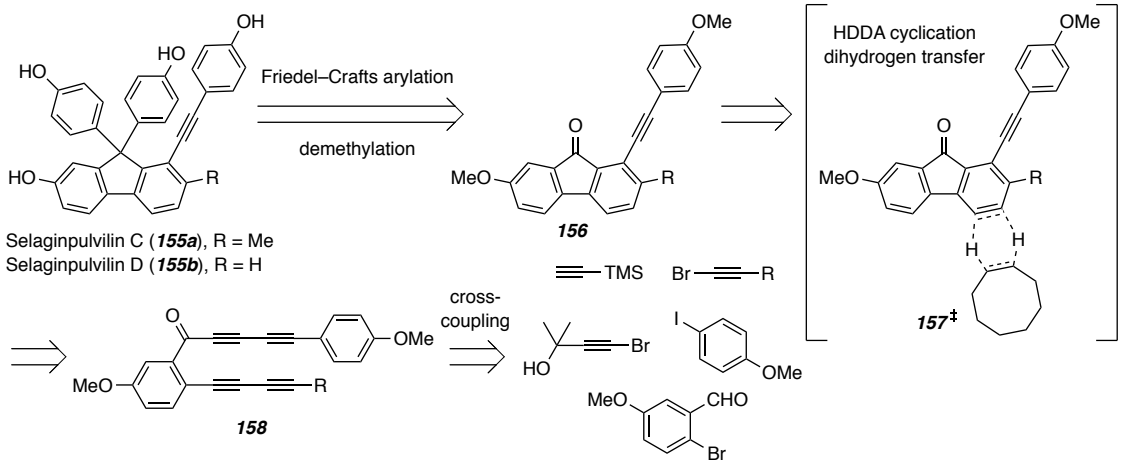

Figure 17. Retrosynthetic analysis of selaginpulvilin C and D by the Lee group.

A total synthesis of selaginpulvilin C (**155a**) and D (**155b**) using HDDA chemistry was published by Lee and co-workers later in the same year (Figure 17).[54] This synthesis highlighted the HDDA reaction to construct the key fluorene intermediate **156** in one

[54] Karmakar, R.; Lee, D. Total Synthesis of Selaginpulvilin C and D Relying on *in Situ* Formation of Arynes and Their Hydrogenation. *Org. Lett*. **2016**, *18*, 6105–6107.

step, followed by a Friedel–Crafts arylation and an overall demethylation. The tetrayne **158** was synthesized by a series of cross-coupling reactions using various fragments.

To make it interesting (rather sad and unfortunate), Dr. Sean Ross and his undergraduate mentee Jacob Kautzky in our lab were working on the same target around the same time with the Lee group, using similar strategy except that the protecting group was different (acetyl vs. methyl). Unfortunately, on the day that Dr. Ross was collecting the NMR spectrum of the intermediate **156**, the total synthesis by the Lee group appeared online.[55]

To summarize, the HDDA cycloisomerization enables new synthetic routes for highly functionalized arene derivatives, and the thermally generated benzyne can turn on new modes of reactivities such as the dihydrogen atom transfer[40] and the aromatic-ene reaction[56]. This reaction is also mechanistically interesting, as it proceeds through a concerted, but highly asynchronous pathway, leading to a benzyne intermediate that is more stable than the polyyne precursor. In the future, this reaction will likely become even more widely used method to construct multisubstituted arene moieties for numerous applications.

[55] This includes an excerpt from Dr. Sean Ross' thesis.
[56] Niu, D.; Hoye, T. R. The aromatic ene reaction. *Nature Chem*. **2014**, *6*, 34–40.

Chapter 2. The Phenol-ene Reaction

Disclaimer: A large portion of the work presented in this Chapter is adopted from a manuscript published in Organic Letters.[57]

2.1 Introduction

Biaryls are one of the common functional groups in organic chemistry. They compose a wide variety of drug and ligand molecules (Figure 18). The most common way of synthesizing biaryls is transition metal catalyzed cross coupling reactions, in which the two aryl-containing components undergo the carbon-carbon bond formation in the presence of a transition metal catalyst. In this chapter, we will describe a transition metal-free biaryl synthesis that involves polyyne precursors and phenolic compounds, via the HDDA reaction cascade followed by a phenol-ene process.[57]

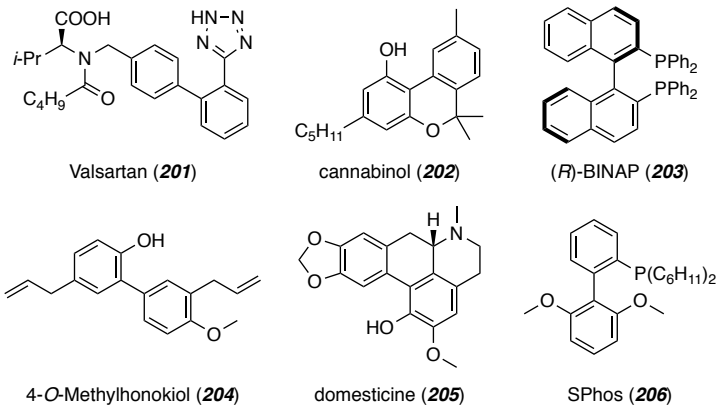

Figure 18. Biaryl moieties in drug and ligand molecules.

Traditionally generated benzyne (**101**) is known to react with phenols via nucleophilic attack of the phenol oxygen atom at the electrophilic benzyne carbon, and subsequent proton transfer to give diaryl ether as the product. This process was first

[57] Zhang, J.; Niu, D.; Brinker, V. A.; Hoye, T. R. The phenol-ene reaction: Biaryl synthesis via trapping reactions between HDDA-generated benzynes and phenolics. *Org. Lett.* **2016**, *18*, 5596–5599.

reported by Dow[58], for conversion of chlorobenzene (**207**) to phenol (**208a**) via **101** (Figure 19a) produces, as the major byproduct, diphenyl ether (**208b**) along with minor amounts of the hydroxylated biphenyls **208c** and **208d**. A more mildly basic variant for benzyne generation, introduced by Kobayashi[13] (Figure 19b), gives diaryl ethers **208e**, as generalized by Larock[59] and subsequent investigators.

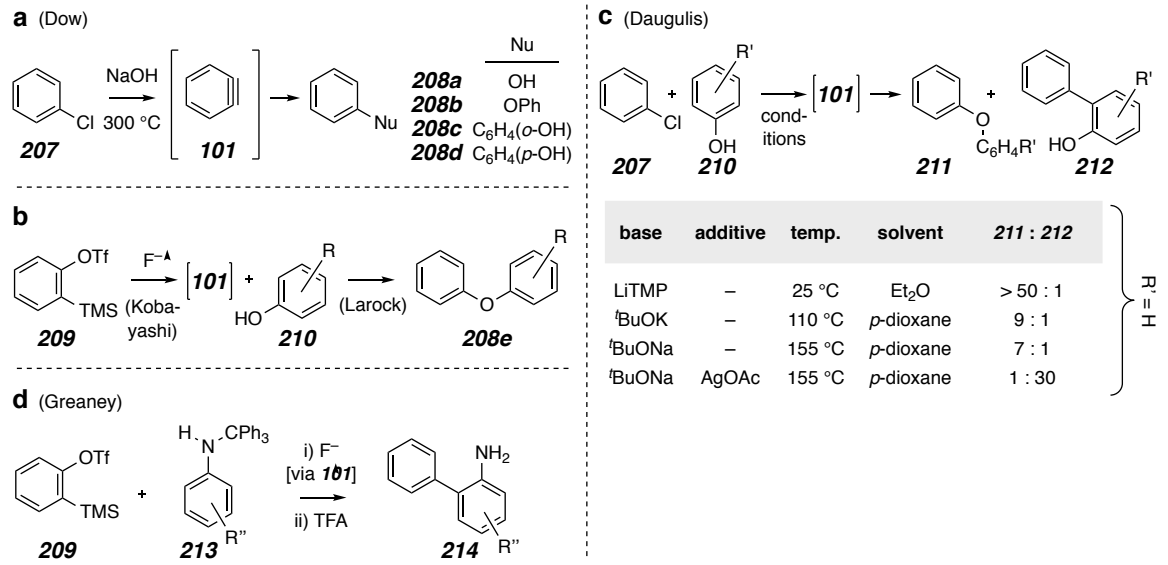

Figure 19. Previous reports of *ortho*-arylation reactions of benzynes.

Daugulis and coworkers have shown that the nature of the phenoxide counterion or the reaction solvent can amplify reactivity at the position *ortho* to the phenolic oxygen, providing an attractive preparative route for accessing *o*-hydroxylated biaryls (Figure 19c).[60] Phenoxides react with *o*-benzyne (**101**) generated under strongly basic conditions to give, predominantly, either diaryl ethers **211** or 2-hydroxybiaryls **212**, depending upon the reaction conditions. If a silver additive is present, the reaction preferentially gives

[58] Hale, W. J.; Britton, E. C. Development of synthetic phenol from benzene halides. *Ind. Eng. Chem.* **1928**, *20*, 114–124.
[59] Liu, Z.; Larock, R. C. Facile *O*-arylation of phenols and carboxylic acids. *Org. Lett.* **2004**, *6*, 99–102.
[60] Truong, T.; Daugulis, O. Divergent reaction pathways for phenol arylation by arynes: synthesis of helicenes and 2-arylphenols. *Chem. Sci.* **2013**, *4*, 531–535.

biaryl **212**. Intramolecular constraints can further enforce reaction to occur at the (proximal) carbon rather than the (distal) oxygen atom of a tethered phenoxide.[61]

We are unaware of any example of the reaction of a neutral phenolic species with an aryne prior to 2012.[29] However, Greaney and coworkers have reported highly selective *ortho*-arylation of aniline derivatives **213** bearing a bulky trityl masking substituent on the nitrogen atom under conditions where the neutral aniline entity is likely the attacking nucleophile (and followed by a cation exchange), to give biaryl **214** (Figure 19d).[62]

2.2 The Phenol-ene Reaction: Discovery and Mechanistic Insights

Benzynes generated thermally by the hexadehydro-Diels–Alder cycloisomerization (of a substrate comprising a 1,3-diyne and a remote, tethered, alkynyl diynophile) are produced (and trapped) in the absence of other extraneous reagents. This allows for exploration of trapping reactions wherein the capture reagent(s) is(are) neutral species. We report here reactions of HDDA benzynes with a variety of phenols to give biaryl products, a class valuable to many different sub-disciplines of organic chemistry.[63]

As an initial example, consider the HDDA cascade (i.e., generation plus *in situ* trapping) between the tetrayne **215** and phenol itself (Figure 20). When heated at 85 °C (in 1,2-dichloroethane) for ca. 16 h, the *o*-hydroxyphenyl-substituted arene **217a** was produced as the major product. This structure was assigned to have the new aryl substituent attached in the position shown on the basis of the chemical shift of the aryl methyl substituent at δ 2.18 ppm. This is significantly further upfield than is typically seen (ca. δ 2.4 ppm) for these protons in analogous compounds that lack an adjacent aryl substituent.[42] This mode of attack by the nucleophilic phenol is consistent with the

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[61] Bajracharya, G. B.; Daugulis, O. Direct transition-metal-free intramolecular arylation of phenols. *Org. Lett.* **2008**, *10,* 4625–4628.
[62] Pirali, T.; Zhang, F.; Miller, A. H.; Head, J. L.; McAusland, D.; Greaney, M. F. Transition-metal-free direct arylation of anilines. *Angew. Chem. Int. Ed.* **2012**, *51*, 1006–1009.
[63] For examples, see: Hussain, I.; Singh, T. Synthesis of biaryls through aromatic C-H bond activation: a review of recent developments. *Adv. Synth. Catal.* **2014**, *356*, 1661–1696.

expected greater electrophilic character at C6 (greater internal bond angle of 138°) in the geometry of intermediate benzyne[42] **216**.[10,11,64,65] None of the product containing a 2-hydroxyphenyl substituent at C7 was observed. The half-life for disappearance of **215** via the initial, rate-limiting cyclization to the fused benzyne **216** is ca. 3 h.

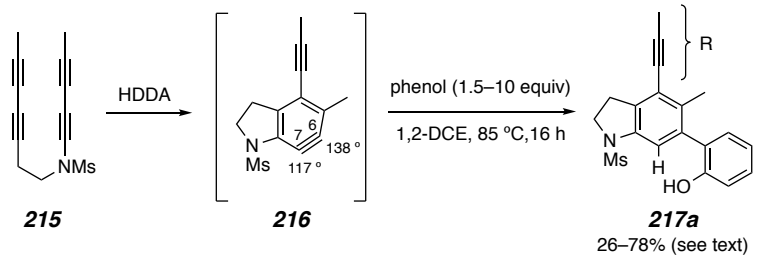

Figure 20. Initial discovery of the phenol-ene reaction.

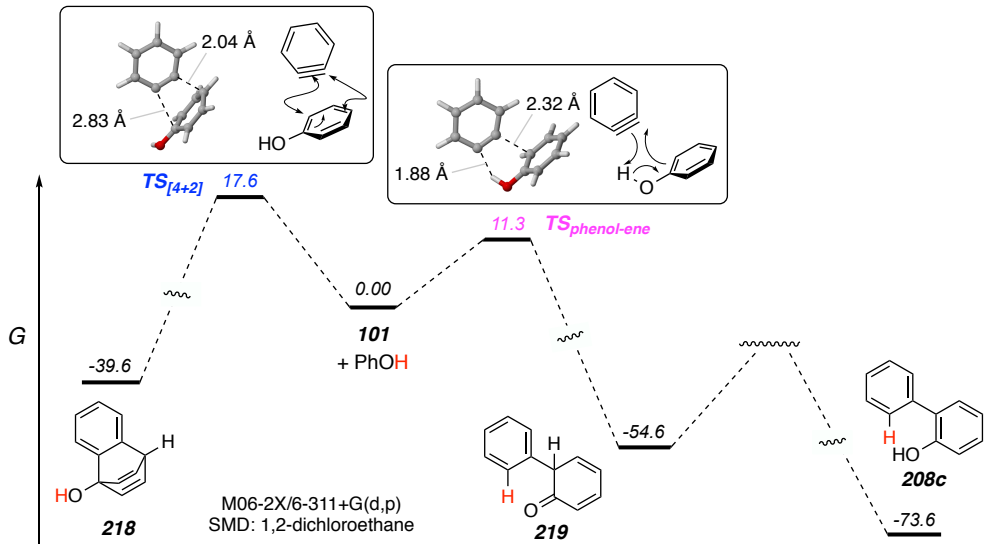

Figure 21. DFT calculation of the phenol-ene process, OH addition, and Diels–Alder reaction pathways.

[64] The distortion of unsymmetrical benzynes has been advanced as a reliable means for rationalizing and predicting the site of greater electrophilic character; namely the *sp*-carbon atom having the larger internal bond angle displays greater *p*-character in the in-plane π-bond.

[65] Hamura, T.; Ibusuki, Y.; Sato, K.; Matsumoto, T.; Osamura, Y.; Suzuki, K. *Org. Lett.* **2003**, *5*, 3551−3554.

We also studied the dependence of this reaction on the number of equivalents of phenol that was used. Through direct analysis (^{1}H NMR; internal standard) of reaction solutions having 1.1, 3.3, and 10 equiv. of phenol at the outset, we observed the "NMR yield" to increase from 35% to 62% to 78%, respectively. This compared well with the isolated yield following chromatographic purification (26% for 1.1 equiv. and 77% for 10 equiv.).

We then envisioned this biaryl-forming trapping reaction to proceed by a mechanism involving concerted transfer of the hydroxyl proton and formation of the C–C bond to C2 of phenol.[66] This can be viewed as a phenol-ene process, reminiscent of the enol-ene (or Conia[67]) reaction.[68] HDDA-benzynes are known to engage in classical Alder-ene type reactions both intra-[43,56] and intermolecularly. The phenol-ene possibility was explored through DFT calculations for the reaction between *o*-benzyne (**101**) and phenol, which leads to the cyclohexadienone **219**, the precursor tautomer of **208c** (Figure 21). We also explored a related process, the [4+2] Diels–Alder cycloaddition reaction between **101** and carbons C1-C4 of phenol, leading to the bicyclic diene **218**. This type of product was seen as a minor component in a few of the phenol-ene reactions we have studied (for example, see $\mathbf{223_{[4+2]}}$ in Figure 23, below). Indeed, a transition state geometry for each of these two pathways was identified. The energy of $\mathbf{TS_{[4+2]}}$ was considerably higher than that of $\mathbf{TS_{phenol\text{-}ene}}$. We conclude that a phenol-ene mechanism is the most likely pathway for formation of the biaryls whose formation we are reporting here (e.g., **216** to **217a**). This view is reinforced by some of the additional results we describe below.

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[66] A reviewer raised the possibility of the intermediacy of an initially formed biaryl ether, since some are known to rearrange to *o*-hydroxybiaryls. This is essentially always effected under photochemical conditions or at high temperature in the presence of very strongly basic agents.

[67] Conia, J. M.; Le Perchec, P. The thermal cyclisation of unsaturated carbonyl compounds. *Synthesis.* **1975**,1.

[68] This phenol-ene process is quite distinct from the thiol-ene "click" reaction prevalent in today's chemical vernacular. Hoyle, C. E.; Bowman, C. N.; Thiol–Ene Click Chemistry. *Angew. Chem. Int. Ed.* **2010**, *49*, 1540–1573.

2.3 Syntheses of Functionalized Biaryls: The Scope of the Phenol-ene Reaction

Shown in Figure 22 are the *o*-hydroxylated biaryl products from a host of other phenolic compounds that we have used to trap benzyne **216**. The indicated yields are of material following chromatographic purification on silica gel. The yields generally reflect the overall cleanliness of the reaction (as judged by ^{1}H NMR analysis of the crude product mixture). In every instance, just 1.5 equivalent of the trapping phenol was used. In view of the concentration dependence described above for the formation of **217a** (Figure 20), the isolated yields of the compounds in Figure 22 would likely increase if larger amounts of the phenolic trapping agents were used.

Products in panel (a) arose from trapping with a series of simple mono-substituted phenols. There is a clear trend that trapping agents with more electron rich arenes capture the benzyne more efficiently. In fact, when *p*-nitrophenol was used, the biaryl product was not detected. Panel (b) shows the results of trapping with hydroquinone (to **217g**), resorcinol (to **217h** and **217i**), and catechol (to **217j**). As with *p*-methoxyphenol (to **217f**), each of these electron-rich benzenediols trapped efficiently.

4-Hydroxyindole and 5-hydroxyindole gave rise to **217k** and **217l**, respectively [panel (c)]. The latter outcome is particularly interesting since there are two possible sites at which the phenol-ene reaction could take place, but only one isomer, **217l**, was observed. Naphthols proved to be particularly good traps [panel (d)]. This likely reflects the reduced amount of aromatic resonance energy that needs to be sacrificed to arrive at the transition state for these phenol-ene reactions. By analogy with many other electrophilic substitution reactions of 2-naphthol, this benzyne trapping occurred exclusively at the 1-position, giving only **217m** via a TS that maximally retains the aromaticity of the bystander benzenoid ring. This thinking also accounts for the

regioselectivity observed for the formation of indole **217l**; here, it is pyrrole aromaticity that is fully retained.

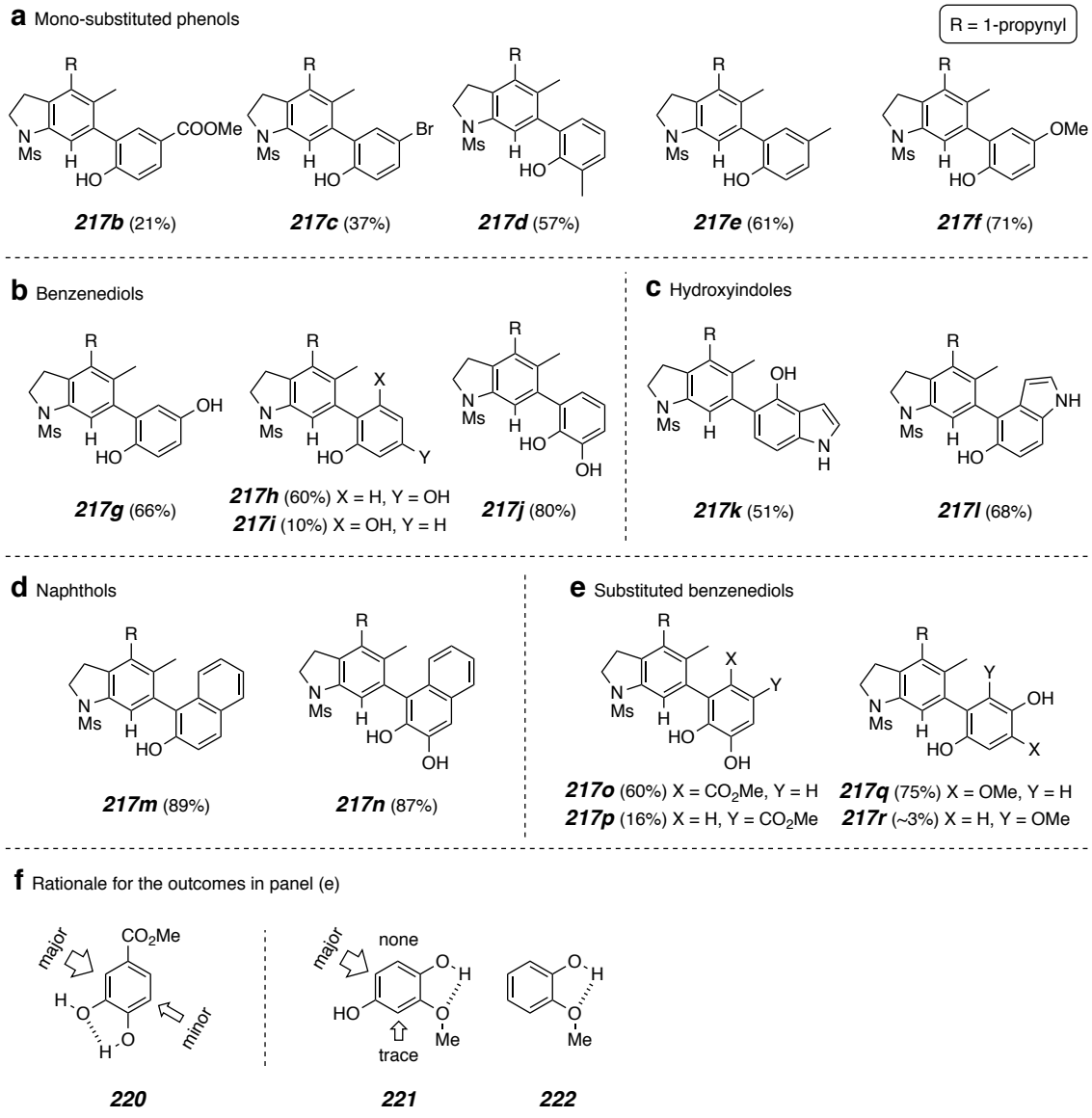

Figure 22. Scope of the phenol-ene reaction with (a) monosubstituted phenols, (b) benzenediols, (c) hydroxyindoles, (d) naphthols, and (e) catechol derivatives. (f) Rationale of the selectivity reported in panel (e).

The reactivity pattern of benzenediols containing a third substituent proved informative [panel (e)]. Methyl 3,4-dihydroxybenzoate (**220**) gave rise to a

preponderance of the (more hindered) adduct **217o** with an ca. 4:1 selectivity over the less hindered **217p**. 2-Methoxyhydroquinone (**221**) gave, predominantly **217q**, along with a very small amount of the isomeric adduct **217r**. A rationale for these selectivities is offered by the graphics in panel (f). In the case of the benzoate ester **220**, the *para*-hydroxyl proton is presumably the more acidic of the two OH groups and, therefore, the better internal hydrogen bond donor.[69] Thus, the arrangement shown in **220** should dominate for this unsymmetrical catechol derivative, leaving the proton of the *meta*-hydroxyl group more available to participate in the phenol-ene reaction. An additional factor could be that the intermediate cyclohexadienone arising from the major ene reaction pathway enjoys a higher degree of conjugation (i.e., a 4-hydroxydienoate) compared to that from the minor pathway.

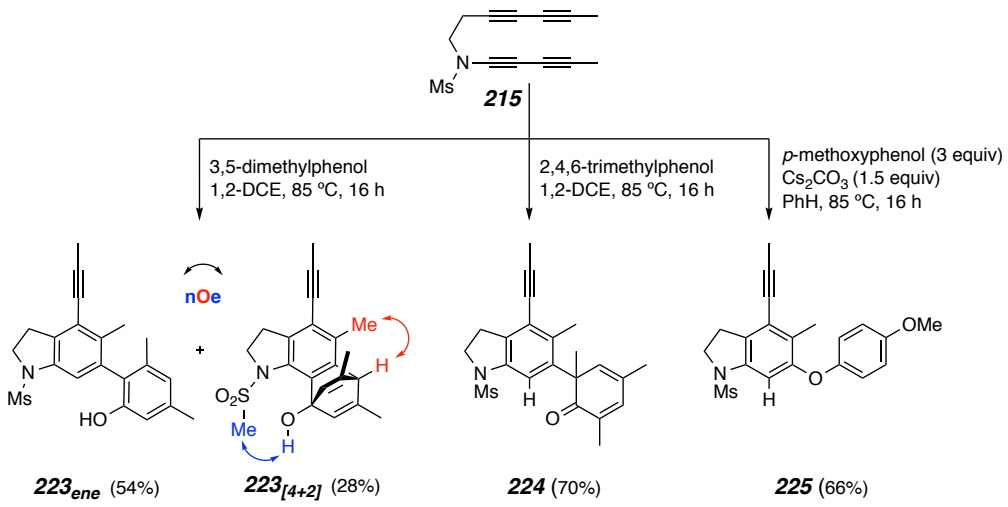

Figure 23. The competing reaction pathways: (a) Diels–Alder reaction, (b) an isolable cyclohexadienone formation, and (c) diaryl ether formation in the presence of a mild base.

[69] Using DFT [M06-2X/6-311+G(d,p)], we computed the energies of **220** and the alternative hydrogen bond isomer (*meta*-OH as the donor) and found **220** to be 1 and 0.7 kcal•mol^{-1} more stable in the gas phase and using 1,2-dichloroethane solvation (SMD), respectively.

In cases where the trapping phenol lacked a substituent in the *para* position, small amounts of [4+2] adducts (i.e., analogs of **218**, Figure 21) were formed. By far the greatest proportion of this type of product was seen using 3,5-dimethylphenol, in which case the phenol-ene and DA adducts $\mathbf{223_{ene}}$ and $\mathbf{223_{[4+2]}}$, respectively, were produced in an approximately 2:1 ratio (Figure 23, left). The *meta*-disposed methyl groups presumably provide a small steric barrier to the approach of **216** to an *ortho* carbon, enroute to the TS leading to the dienone precursor of $\mathbf{223_{ene}}$.

Two additional experiment was performed to test the reactivity with 2,4,6-trimethylphenol (no *o*-proton for rearomatization, Figure 23, entry 2) and to probe the effect of the presence of a basic reagent (Figure 23, entry 3). When trapping with 2,4,6-trimethylphenol, the benzyne **216** gave rise to the dienone **224** in 70% yield. This is essentially a *de novo* method of synthesizing conjugated cyclohexadienones. In the latter case, tetrayne **215** was heated with 4-methoxyphenol in the presence of a suspension of Cs_2CO_3 in benzene. This substantially redirected the course of reaction; the diaryl ether **225** was formed in 66% yield and none of the biaryl **217f** (Figure 22) was observed. This result highlights the difference(s) that can arise in aryne trapping reactions under basic vs. neutral reaction conditions, hallmarks of classical vs. HDDA protocols for benzyne generation, respectively.

Finally, to establish that the phenol-ene reaction is not limited to benzyne **216**, we have trapped the HDDA benzynes derived from precursors **226**, **144**, and **139a** with 4-methoxyphenol (Figure 24). The electron-deficient benzyne from **226** as well as those derived from the symmetrical tetraynes **144** and **139a** give the biaryl products **227–229** as the major product. A minor isomer of **229'**, having the new biaryl linkage to C4' rather than C5', was also formed (**229**:**229'** = 6:1). The benzyne derived from **139a** has also been observed to react with reduced regioselectivity with other classes of nucleophiles due to smaller benzyne distortion angle.

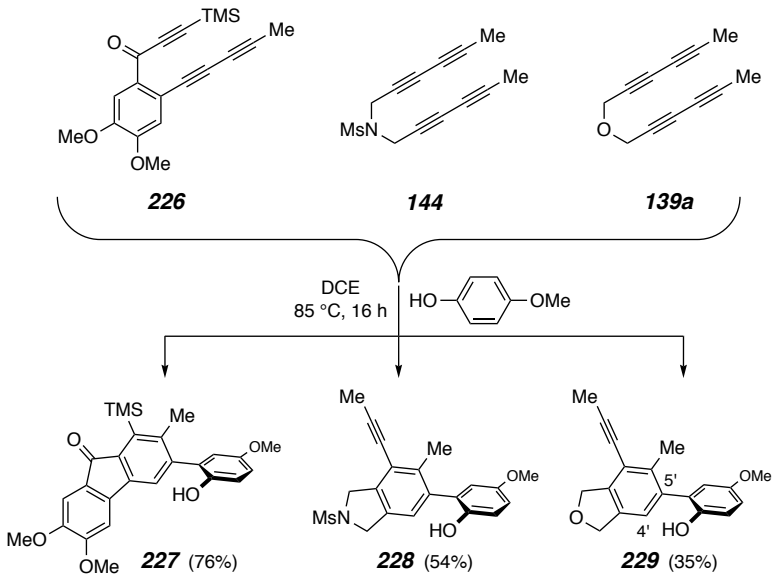

Figure 24. Phenol-ene reaction involving other type of thermally generated benzynes.

2.4 Summary

In summary, we have demonstrated that a variety of phenolic compounds react with thermally generated benzynes (and in the absence of any basic or metal-containing agents) at the carbon *ortho* to the phenolic hydroxyl group to produce 2-hydroxybiaryl derivatives. DFT computation suggests that this can occur through a concerted, 6-membered transition structure that we have referred to here as a "phenol-ene" reaction. The more electron-rich the phenol is, the better reactivity. The selectivities observed with several more complex, substituted phenols (phenolic compounds) can also be rationalized by this mechanistic model of the process.

Chapter 3. Reaction of HDDA-generated Benzynes with *N*-Heterocycles

Disclaimer: A large portion of the work presented in this Chapter is adopted from a manuscript submitted to Chemical Science.[47] This work is the collaboration results from Mr. Sahil Arora and the author of this Thesis, in which the author of this Thesis contributed all the computational studies as well as the development of the first part (Mode A) of the manuscript. The discussion of the three-component coupling results (Mode B and C) will not be presented in this chapter.

3.1 Previous Reports of Benzyne Trapping with *N*-Heterocycles

In earlier work, we reported novel three-component coupling reactions (TCRs) initiated by the reaction of the benzyne with cyclic sulfides[42] or tertiary amines,[45,46] including alkaloidal natural products.[51] A natural extension was to investigate whether *N*-heterocyclic arene compounds ("*N*-hetaryls", *N*-HARs) would engage in TCRs. Classically generated benzynes (**101**, i.e., those formed by way of various *ortho*-elimination reactions of precursor arenes)[12,52,70] are known to undergo trapping reactions with one of the 6-membered *N*–heterocycles **301** such as pyridine, quinoline, or isoquinoline (Figure 25).[71,72,73,74] These reactions are presumed to be initiated by attack of the nucleophilic nitrogen atom in the heterocycle onto the electrophilic aryne, producing a 1,3-zwitterion (cf. **302**). In those studies, aliphatic nitriles, terminal alkynes, and various

[70] Kitamura, T. Synthetic Methods for the Generation and Preparative Application of Benzyne. *Aust. J. Chem*. **2010**, *63*, 987−1001.
[71] Jeganmohan, M.; Cheng, C. H. Reaction of arynes, *N*-heteroaromatics and nitriles. *Chem. Commun.,* **2006**, 2454–2456.
[72] Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C. H. Synthesis of *N*-arylated 1,2-dihydroheteroaromatics through the three-component reaction of arynes with *N*-heteroaromatics and terminal alkynes or ketones. *Chem. Asian. J.,* **2010**, *5,* 153–159.
[73] Bhunia, A.; Roy, T.; Pachfule, P.; Rajamohanan, P. R.; Biju, A. T. Transition-metal-free multicomponent reactions involving arynes, *N*-heterocycles, and isatins. *Angew. Chem., Int. Ed.* **2013**, *52*, 10040−10043.
[74] Bhunia, A.; Porwal, D.; Gonnade, R. G.; Biju, A. T. Multicomponent reactions involving arynes, quinolines, and aldehydes. *Org. Lett*. **2013**, *15*, 4620−4623.

carbonyl compounds were used as third components to trap the zwitterion, giving rise to heteroaromatics **303** and **304**.

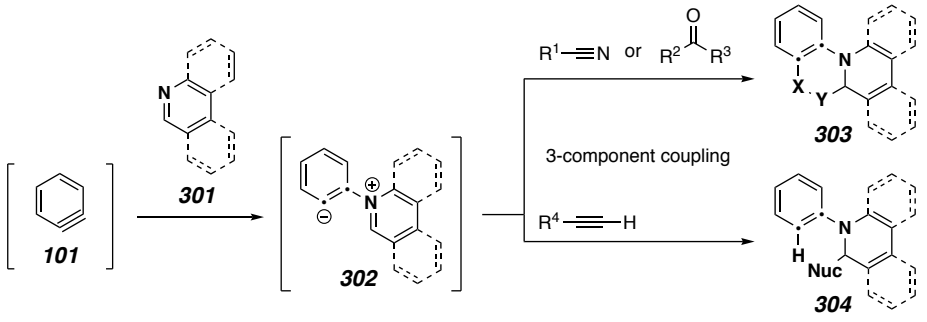

Figure 25. Three-component coupling reactions (TCRs) between traditionally generated benzyne and 6-membered *N*-heterocycles.

3.2 New Mode of Reactivity between *N*-HARs and HDDA-generated Benzynes

We were interested in learning the fate of this zwitterionic species **302** (cf. **307**, from the HDDA-generated benzyne **306**, Figure 26) in an HDDA reaction manifold both in the absence as well as presence of potential third-component reactants. We herein report that upon formation of **307**, a variety of reaction pathways can ensue—some precedented and some not. The reactions of a zwitterion like **307** that we have observed can be categorized into three modes. Mode A leads to products that are 1:1 adducts between **306** and the *N*-HAR. In mode B, in situ bimolecular reaction of zwitterion **307** with an electrophile **308** of type **X**=**Y** as a third component forms a new 6-membered ring in products **310**. In mode C, protonation of **307** by a Brønsted acid [i.e., an in situ protic nucleophile (H–Nuc), the third component] and collapse of the nascent Nuc^{-}/$iminium^{+}$ ion pair produces adducts **311**. The full roster of reactants used in the studies we report here are compiled in Figure 27.

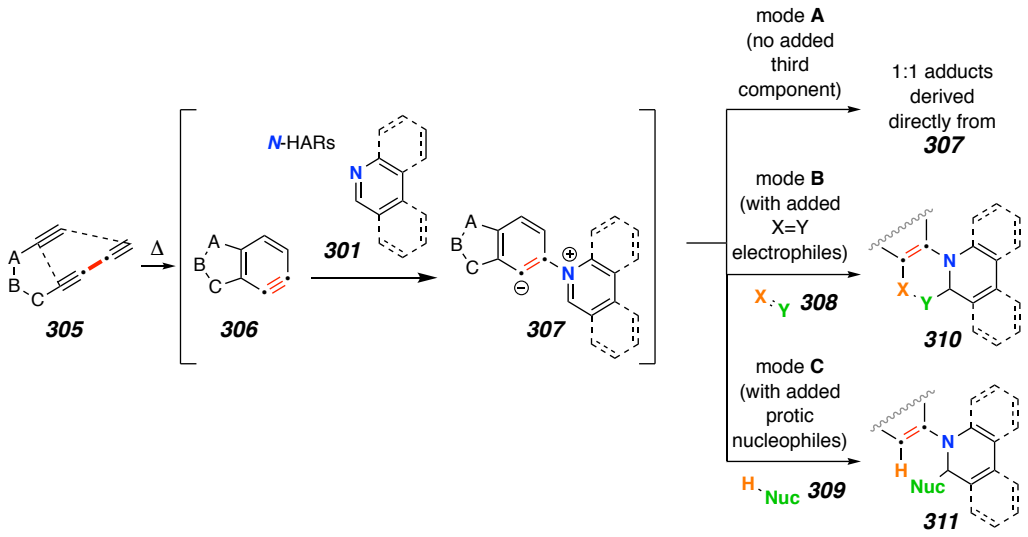

Figure 26. Divergent reactivity between HDDA-generated benzyne and 6-membered *N*-heterocycles.

Mode A, formation of an isolable 1:1 adduct between the aryne and *N*-HAR, has received very little previous attention. In the only two relevant studies that we can locate, (i) Fields and Meyerson (1966[75]) speculated on the intermediacy of [2+2]-addition products from arynes and pyridine on the basis of gas chromatographic and mass spectrometric analyses of complex product mixtures formed when, for example, phthalic anhydride, a benzyne precursor, was pyrolyzed in the presence of pyridine; and (ii) Biju and co-workers observed 2-pyridone products when classically generated benzynes were allowed to be captured by pyridine (cf. formation of **314** via carbene **315**, Figure 28).[73]

As a point of departure for benchmarking the HDDA chemistry, we examined reactions of the triyne substrate **226** (see Figure 27) with several *N*-HARs in the absence of any added, potential third component. For example, when a benzene solution of **226** was heated to 85 °C in the presence of isoquinoline (**301a**), the four-membered

[75] Fields, E. K.; Meyerson, S. Arynes by Pyrolysis of Acid Anhydrides. *J. Org. Chem.* **1966**, *31*, 3307–3309.

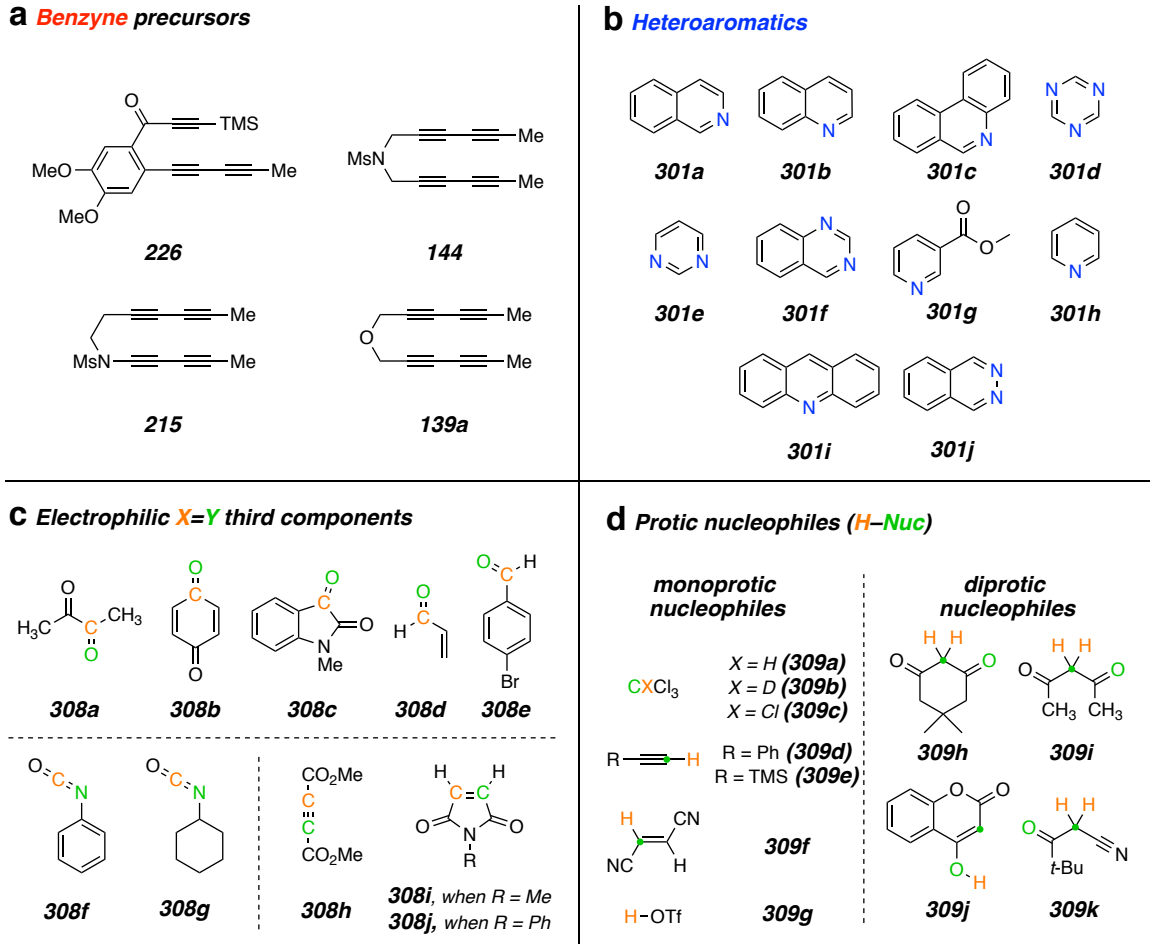

Figure 27. List of all reactants used in this study: **(a)** benzyne polyyne precursors; (**b)** *N*-heteroaromatics (*N*-HARs); **(c)** activated electrophiles; and **(d)** protic–nucleophiles.

benzoazetidine **313** and 2-isoquinolone **314** were formed (Figure 28) by in situ trapping of **316** by **301a**. Because of the likely oxidative lability of product **313**, it was found to be unstable under ambient conditions and needed to be characterized immediately after isolation. Isoquinolone **314** was formed presumably via the *in situ* air oxidation of carbene **315**.

The pathways leading to each of these products were then studied using DFT calculations of the reaction between a simplified aryne [3,6-dimethylbenzyne (**323**)] and isoquinoline (**301a**) (Figure 29). The formation of **313** can be explained by a net

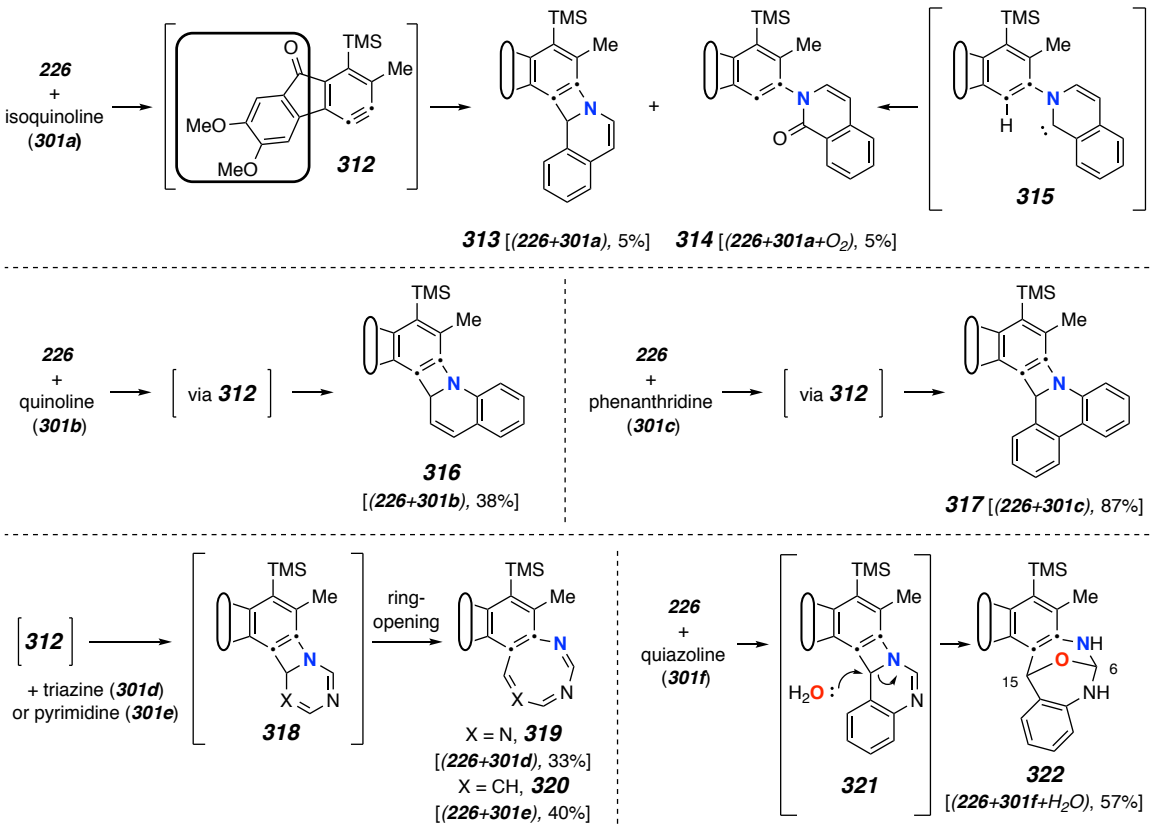

Figure 28. Trapping of the benzyne **312** (from **226**, Figure 27) with *N*–hetaryls of the pyridine family (i.e., pyridine, quinoline, isoquinoline, phenanthridine, pyrimidine, 1,3,5-triazine, and quinazoline) follow different reaction pathways.

[2+2]-addition of **301a** to the benzyne, a process involving simple cyclization of the initial zwitterion (cf. **324** to **326**). Formation of **314**, on the other hand, can be rationalized by an intramolecular proton-transfer within the initially formed 1,3-zwitterion **324** and subsequent oxidation of the resulting carbene **325** by oxygen.[76,77,78] This type of reactivity was earlier observed by Biju and coworkers.[73] It is notable that the

[76] Wanzlick, H.-W.; Schikora, E. Ein nucleophiles Carben. *Chem. Ber*. **1961**, *94*, 2389–2393.
[77] Wanzlick, H.-W. Nucleophile Carben-Chemie. *Angew. Chem*. **1962**, *74*, 129–134; Aspects of Nucleophilic Carbene Chemistry. *Angew. Chem. Int. Ed*. **1962**, *1*, 75–80.
[78] Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. Chemical Reactions of the Stable Carbene 1,3,4-Triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene. *Liebigs Ann*. **1996**, 2019–2028.

energies of the DFT transition structures for these two competing pathways (i.e., $\mathbf{TS}_{\text{ringclosing}}$ vs. $\mathbf{TS}_{\text{protonshift}}$) are quite similar. The computations also suggest that electrocyclic ring-opening of the benzoazetidine **326** to the 8-membered benzoazocine derivative **327** is both endergonic as well as a high-barrier process, the latter reflecting, at least in part, the loss of benzenoid aromaticity that is fully revealed in structure **327**.

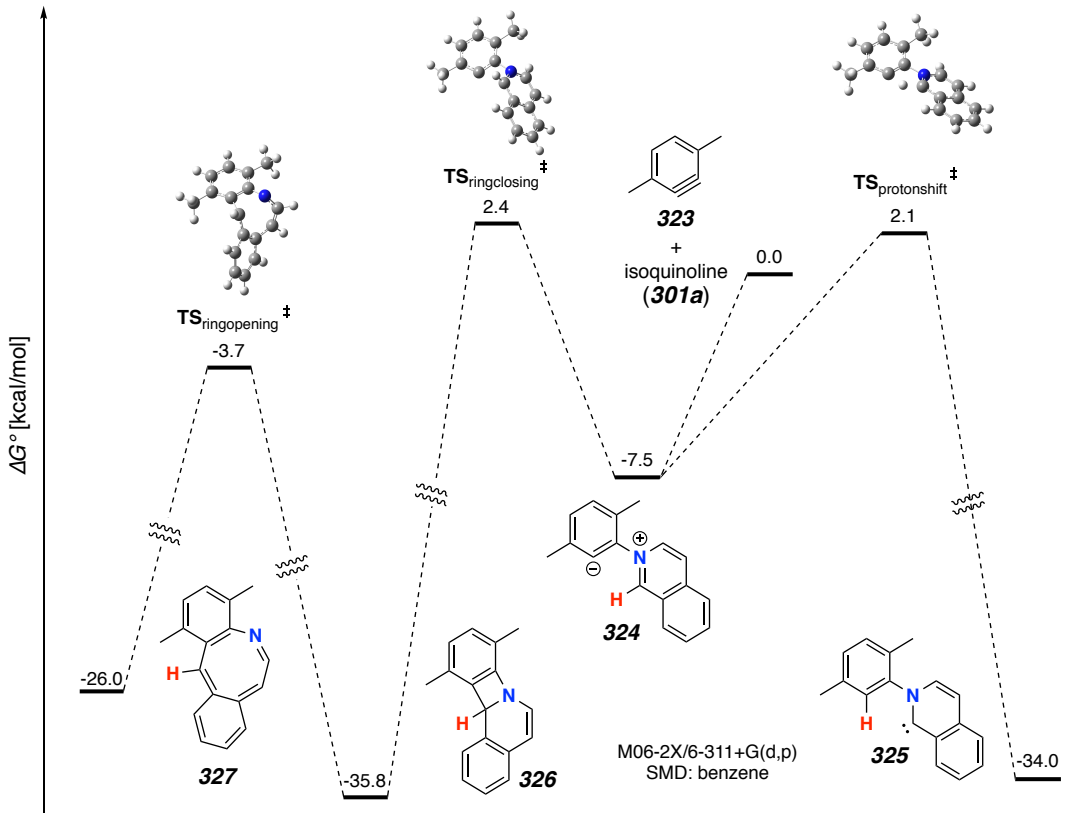

Figure 29. DFT study for **323** + **301a** showing competitive formation of **325** and **326** and a high barrier for ring opening of **326** to the azocine **327**.

Trapping of the benzyne **312** with quinoline (**301b**) led to the isolation of only the four-membered species **316** (cf. Figure 28). This compound also was seen to degrade upon storage for extended periods of time. When phenanthridine (**301c**) was used as the *N*-HAR, the yield of the analogous trapping product **317** was significantly higher (87%) than that of **313** or **316**. The quinolone product (analogous to cf. **315**) was not detected,

and DFT study (Figure 30) suggested that the $TS_{protonshift}$ is about 2.3 kcal•mol^{-1} higher than $TS_{ringclosing}$, causing the selectivity towards the [2+2]-cyclization. The 8-membered ring formation is also a high barrier process (+29.6 kcal•mol^{-1}).

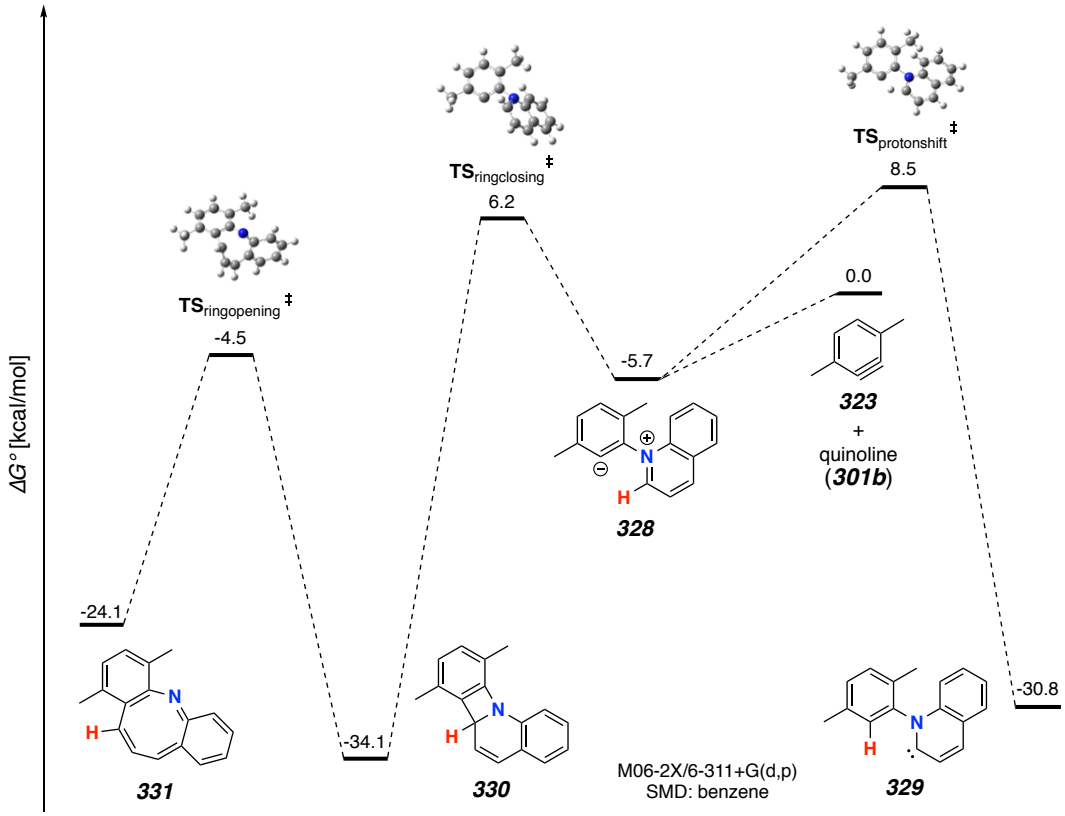

Figure 30. DFT study for **323** + **301b** showing formation of **329** and **330** and a high barrier for ring opening of **330** to the azocine **331**.

Reactions with monocyclic *N*-HARs containing two or more nitrogen atoms proved interesting. 1,3,5-Triazine (**301d**) gave rise to the 1,3,5-triazocine derivative **319** (cf. Figure 28);[79] we can locate only a handful of examples of this (fully unsaturated) heterocycle, and they all bear an amino substituent on the carbon atom between two

[79] These novel 8-membered heterocycles (**319** and **320**) were fully supported by two-dimensional NMR spectroscopic correlations. Additionally, these structural assignments were also validated using the predicted ^{1}H and ^{13}C chemical shifts. See supporting information (SI) for details.

nitrogen atoms (i.e., guanidines).[80,81,82] Compound **319** presumably arises from ring opening of an initially formed, four-membered, [2+2]-adduct analogous to **318**. In this case, that strain-relieving event is not accompanied by loss of aromaticity, as would be the case for the opening of any of **313**, **316**, or **317**. DFT calculations (Figure 31) suggest that the electrocyclic ring-opening of **334** has both an accessible activation barrier ($\Delta G^{\ddagger}$ = 20.7 kcal•mol^{-1}) as well as a favourable exergonicity ($\Delta G°$ = –17.1 kcal•mol^{-1}), in contrast to the conversion of **330** to **331** ($\Delta G°$ = +10 kcal•mol^{-1}). It is also noteworthy that the carbene formation process is higher in energy than the ring-closing event (cf. $TS_{protonshift}$ vs. $TS_{ringclosing}$, $\Delta G^{\ddagger}$ = +3.5 kcal•mol^{-1}), suggesting less favourable carbene formation.

Pyrimidine (**301e**) reacted by a similar pathway to produce **320**, preferring to close to C4 rather than C2 to give **318** (cf. Figure 28). The closure of **318** at C4 maintains some of the N1-C2-N3 growing amidine character and stabilization throughout the reaction coordinate, which would be lost if cyclization were to take place at C2. Again, the diazocine **320** represents a relatively rare class of heterocycle, examples appearing in only four reports.[83,84,85,86]

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[80] Furukawa, M.; Kojima, Y.; Hayashi, S. Reaction of Biguanides and Related Compounds. IV. Reaction of Arylbiguanide with Benzoylacetone in the Presence of a Small Amount of the Arylbiguanide Hydrochloride. *Chem. Pharm. Bull.* **1972**, *20*, 927–930.

[81] Saied, T.; Jelaiel, N.; Efrit, M. L.; Fort, Y.; Comoy, C. Convenient synthesis of substituted benzo[*e*][1,2,4]- or [*d*][1,2,6]oxadiazepines, benzo[*f*][1,3,5]triazocines from *N*-aryliminoesters. *Tetrahedron* **2017**, *73*, 1489–1494.

[82] Perlmutter, H. D. 1,2-Diazocines, 1,3-Diazocines, Triazocines, and Tetrazocines. *Adv. Heterocycl. Chem.* **1990**, *50*, 1–83.

[83] Kumar, R. N.; Suresh, T.; Dhanabal, T.; Mohan, P. S. Utility of Vilsmeier Haack reagent in the synthesis of 3-amino-12-chloroquino[3,2-*e*][1,3]diazocines. *Indian J. Chem. B* **2004**, *43*, 846–851.

[84] Bruni, F.; Costanzo, A.; Selleri, S.; Guerrini, G.; Giusti, L.; Martini, C.; Lucacchini, A. *Farmaco* **1993**, *48*, 309–319.

[85] Miyashita, A.; Taido, N.; Sato, S.; Yamamoto, K.-i.; Ishida, H.; Higashino, T. Ring Transformation of Condensed Pyrimidines by Enamines and Ynamines. Formation of Condensed Pyridines and Condensed Diazocines. *Chem. Pharm. Bull.* **1991**, *39*, 282–287.

[86] Kaminski, V. V.; Comber, R. N.; Wexler, A. J.; Swenton, J. S. Anion-mediated fragmentation reactions. Mechanistic and synthetic aspects of the fragmentation and rearrangement reactions of pyrimidinedione-alkyne photoadducts. *J. Org. Chem*. **1983**, *48*, 2337−2346.

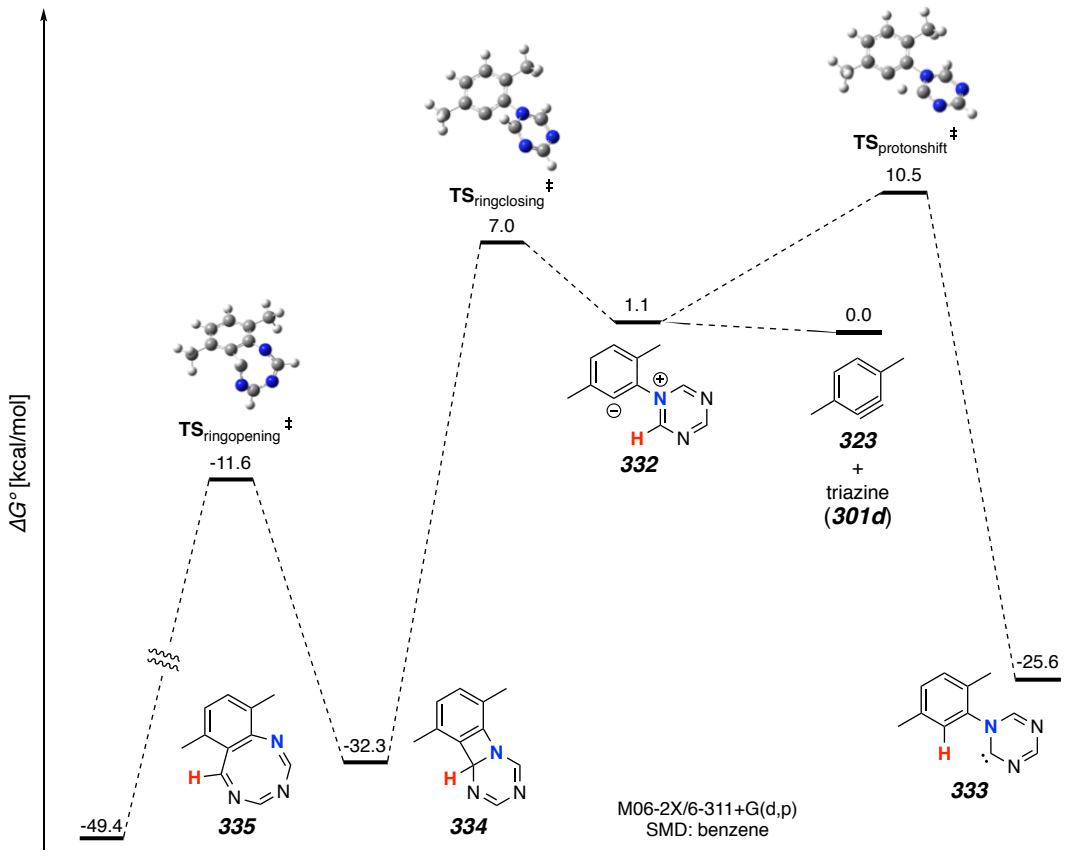

Figure 31. DFT study for **323** + **301d** showing that the formation of azocine **331** is energetically accessible.

Finally, quinazoline (**301f**) gave rise to the unusual adduct **322**, incorporating a molecule of adventitious water (cf. Figure 28). We suggest that in this instance, ring-opening of the initial benzoazetidine **321** is assisted by water, the C–N bond being weakened by virtue of the amidine character of **321** that is absent in the benzoazetidines from quinoline (**301b**) or isoquinoline (**301a**, cf. **313**). The structure assignment of **322** was secured by the clear HMBCs observed for both H6 (δ 6.18 ppm) to C15 (δ 66.8) and H15 (δ 6.67) to C6 (δ 82.1) as well as the chemical shifts of those four nuclei.

3.3 Summary

In this chapter, we have demonstrated that when *N*-heterocyclic compounds are the only trapping agent present, the HDDA-generated benzynes can enable unprecedented and divergent reactivity. The zwitterion generated by the benzyne trapping event leads to different pathways, which give rise to carbene (cf. **314**), benzoazetidine (cf. **313**, **316**, **317**), and benzoazocine (cf. **319**, **320**) formation. DFT calculation supported the mechanistic study and suggested that the benzoazocine formation is both accessible and exergonic with monocyclic *N*-HARs containing two or more nitrogen atoms.

Chapter 4. An Atypical Mode of [3+2]-Cycloaddition

Disclaimer: A large portion of the work presented in this Chapter is adopted from a manuscript published recently in Organic Letters.[87]

4.1 Reactions between Benzynes and Thiocarbonyl-containing Compounds

Thiocarbonyl compounds are known to trap traditionally generated benzynes. Nakayama *et al.* reported that trithiocarbonates can react with Kobayashi benzyne in a net [3+2]-fashion to generate cyclic sulfonium salts[88,89] and dithiocarbamate can directly undergo 1,3-dipolar cycloaddition with benzyne.[90] However, we are unaware of any net [3+2]-cycloaddition reactions between benzynes and thioamides.

We recently reported reactions between benzynes such as **402** (thermally generated from **401**) and aromatic thioamides such as **403** to produce dihydrobenzothiazines such as **405 (**Figure 32).[91] We rationalized this process as proceeding through the series of intermediates **404a**–**404d**. With this in mind, we have been surprised to now see an alternative type of product (and mode of reaction) to arise upon heating **226** in the presence of electron deficient thioamides such as **406a**. This produced, instead, the dihydrobenzothiazole **408**. We propose that this transformation proceeds by a rare type of

[87] Zhang, J.; Page, A.; Palani, V.; Chen, J.; Hoye, T. R. An atypical mode of [3+2]-cycloaddition: Pseudo-1,3-dipole behavior in reactions of electron-deficient thioamides with benzynes. *Org. Lett.* **2018**, *20*, 5550−5553.
[88] Nakayama, J.; Kimata, A.; Tanikuchi, H.; Takahashi, F. Reactions of benzyne with 1,3-benzodithiole-2-thione and related compounds: formation of novel tetracyclic sulfonium salts and their reactions leading to dibenzo-1,3,6,-trithiocin derivatives. *Bull. Chem. Soc. Jpn.* **1996**, 2349–2354.
[89] Nakayama, J.; Kimata, A.; Tanikuchi, H.; Takahashi, F. Reactions of 1,3-benzodithiole-2-thione and ethylene trithiocarbonate with benzyne generated from 2-carboxybenzenediazonium chloride: preparation of novel bicyclic sulfonium salts by trapping 1,3-dipolar cycloaddition intermediates. *Chem. Comm.* **1996**, 205–206.
[90] Hwu, J. R.; Hsu, Y. C. Stereospecific benzyne-induced olefination from β-amino alcohols and its application to the total synthesis of (-)-1-deoxy-D-fructose *Chem. Eur. J.* **2011**, 4727–4731.
[91] Palani, V.; Chen, J.; Hoye, T. R. Reactions of HDDA-derived benzynes with thioamides: Synthesis of dihydrobenzothiazino-heterocyclics. *Org. Lett.* **2016**, *18*, 6312–6315.

net [3+2]-cycloaddition to produce ammonium ylide[92,93] **407b**, followed by ethylene elimination.

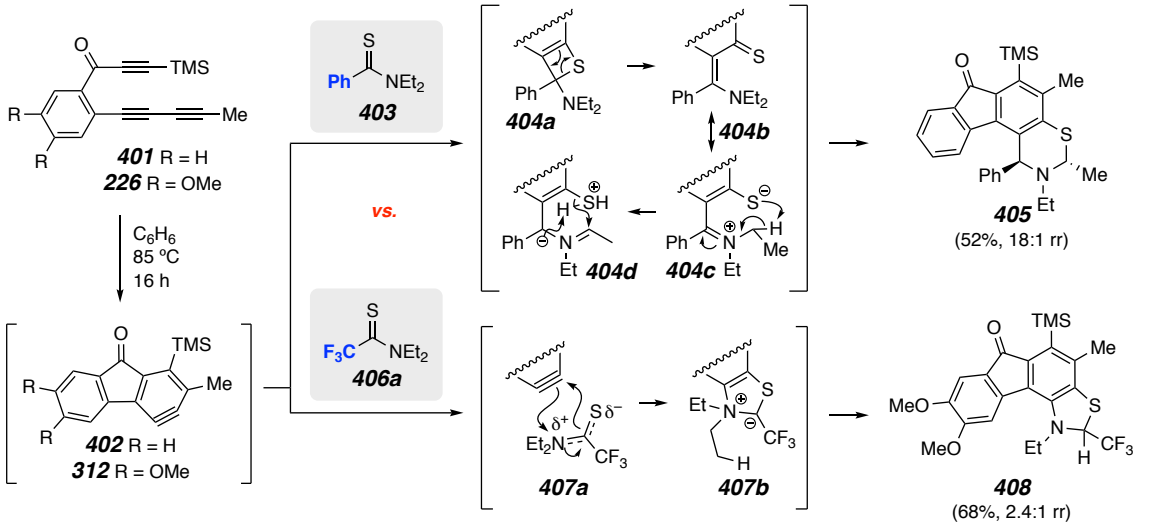

Figure 32. Previous and current work reporting divergent (top. Vs. bottom, respectively) behavior in the trapping reactions of benzynes with thioamides.

Although the reaction between **312** and **406a** may evoke the notion of a 1,3-dipolar cycloaddition,[94,95,96,97,98] it differs in important ways. More specifically, each of the non-sacrificial resonance contributors of classical 1,3-dipoles has the same overall bond order, regardless of whether it is of the allyl or propargyl type (Figure 33). Each is a zwitterionic species with a formal positive charge on the central atom and negative charge on one of

[92] Clark, J. S. In *Nitrogen, Oxygen and Sulfur Ylide Chemistry*, Ed., Oxford University Press, Oxford, 2002.
[93] Wittig, G. Achievements and problems in ylid chemistry. *J. Organomet. Chem.* **1975**, *100*, 279–287.
[94] Ikawa, T.; Masuda, S.; Takagi, A.; Akai, S. 1,3- and 1,4-Benzdiyne equivalents for regioselective synthesis of polycyclic heterocycles. *Chem. Sci*. **2016**, *7*, 5206−5211.
[95] Ikawa, T.; Kaneko, H.; Masuda, S.; Ishitsubo, E.; Tokiwa, H.; Akai, S. Trifluoromethanesulfonyloxy-group-directed regioselective (3 + 2) cycloadditions of benzynes for the synthesis of functionalized benzo-fused heterocycles. *Org. Biomol. Chem*. **2015**, *13*, 520–526.
[96] Li, P.; Zhao, J.; Wu, C.; Larock, R. C.; Shi, F. Synthesis of 3-substituted indazoles from arynes and *N*-tosylhydrazones. *Org. Lett*. **2011**, *13*, 3340–3343.
[97] Spiteri, C.; Keeling, S.; Moses, J. E. New synthesis of 1-substituted-1*H*-indazoles via 1,3-dipolar cycloaddition of *in situ* generated nitrile imines and benzyne. *Org. Lett.* **2010**, *12*, 3368–3371.
[98] For a recent review that includes a subsection compiling 1,3-dipolar cycloaddition reactions, see Wu, C.; Shi, F. A closer look at aryne chemistry: Details that remain mysterious. *Asian J. Org. Chem*. **2013**, *2*, 116–125.

its terminal atoms.[99] The [3+2]-cycloaddition products that arise from engagement of a 1,3-dipole with the π-bond of a dipolarophile are, formally, uncharged at all atoms in the principal resonance contributor of the newly created five-membered ring. The nature of **406a** as well as its conversion to the ylide **407b** are just the opposite—that is, **406a** does not meet the definition of a 1,3-dipole, and now, the resulting adduct **407b** is zwitterionic.

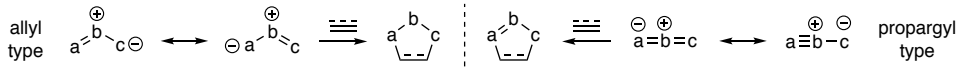

Figure 33. Examples of 1,3-dipoles and 1,3-dipolar cycloadditions.

4.2 Pseudo 1,3-Dipolar Cycloaddition between HDDA-derived Benzynes and Electron-withdrawing Thioamides: Mechanistic Study and Substrate Scope

We turned to DFT calculations to help further assess this novel type of [3+2]-cycloaddition (Figure 34). The computed reaction profile (with minima represented by **101**, **406a**, **409**–**410** and transition structures by **TS1** and **TS2**) for the model addition of *N,N*-diethyltrifluorothioacetamide (**406a**) to *o*-benzyne (**101**) is shown in Figure 34. The computed exergonicity for the formation of the ammonium ylide **409** as well as for its further conversion to **410** and ethylene (ca. 20 and 50 kcal•mol^{-1}, respectively) are notable. We identified a transition structure (**TS1**) corresponding to a low barrier process for a concerted cycloaddition of **406a** to **101**. The geometry of that TS suggests that the addition proceeds with the nucleophilic portion of the thioamide leading the way—that is, the carbon-sulfur bond formation is more advanced than that of the carbon-nitrogen (cf. indicated bond lengths in **TS1** vis-à-vis those in **409**). The 1,2-zwitterion character in **409** sets up a facile intramolecular elimination reaction via **TS2** to produce **410**, the simplified

[99] Huisgen, R. 1,3-Dipolar Cycloadditions–Introduction, Survey, Mechanism. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A. Ed.; Wiley: New York, 1984; Vol. 1, pp 3–6.

analog of **408**, and ethylene. The low activation barrier for this step (ca. 15 kcal•mol^{-1}) is also notable. We also computed the reaction energy for the transformation of the analog of **406a** in which the CF_3 substituent was replaced with a CH_3 group to give the CH_3 analog of **409**. That step is less exergonic (5 kcal•mol^{-1}) than that of **406a** to **409**. Whereas it was a trivial matter to locate **TS1**, we have been unable to identify a bound TS for the case of the methyl analog. The presence of the electron-withdrawing substituent in the model thioamide **406a** appears to play an important role.

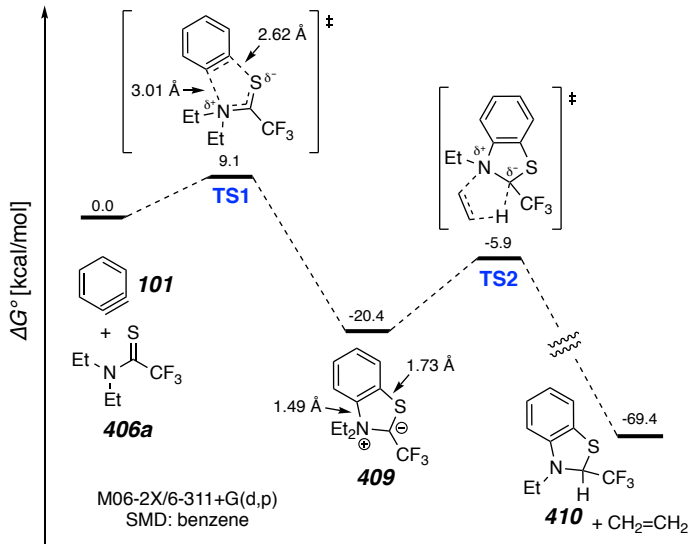

Figure 34. DFT calculations for the 1,3-dipolar cycloaddition and subsequent elimination between *o*-benzyne (**101**) and diethyl thioamide **406a**.

To gain direct experimental evidence for the ejection of an alkene from an ylide such as **407b** (or **409**), we studied the reaction of triyne **226** and *N,N*-dioctyltrifluorothioacetamide (**406b**, Figure 35). A 2.2:1 ratio of the isomeric *N*-octylbenzothiazolines **412** and **413** was formed. In addition, a very nearly equimolar ratio of 1-octene was observed in the crude reaction mixture (^{1}H NMR and GC-MS). This result is consistent with the eliminative fragmentation shown in species **411**.

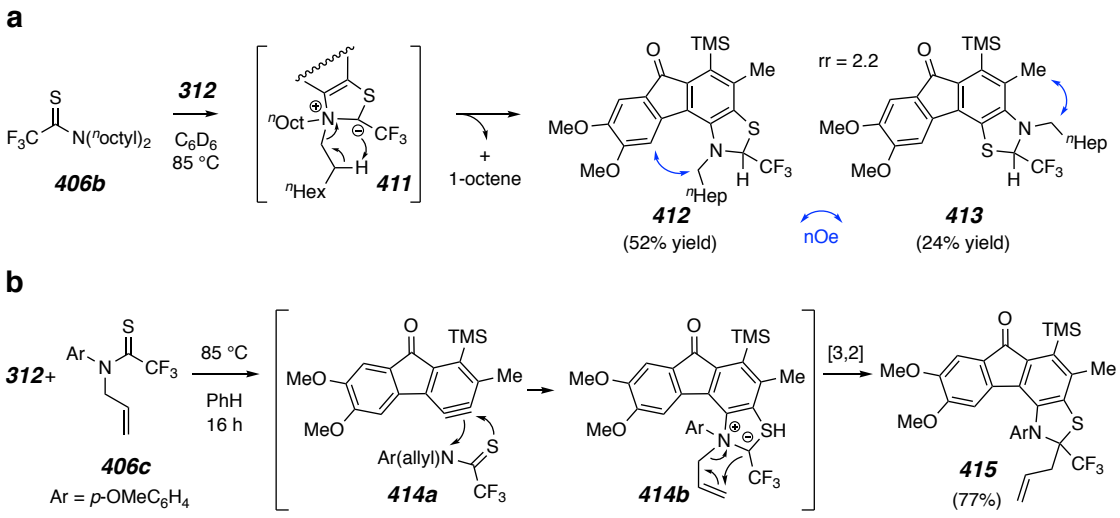

Figure 35. (a) Use of the *N,N*-dioctylthioamide **406b** allowed identification of 1-octene, the elimination product from **411**, and led to the structural assignment of the major and minor products **412** and **413**, respectively, by the indicated nOe's. (b) Product **415** from [3,2]-sigmatropic rearrangement also support the intermediacy of ylide **414b**.

To further clarify, in many of the reactions reported here, two constitutional isomers were formed, arising from competitive modes of addition of the thioamide to the various unsymmetrical benzynes. The assignment of constitution to the major and minor isomers **412** and **413** rests on the nOe's shown in blue in Figure 35a. For many of the additional isomeric pairs (ratios indicated as rr), only the major isomer is shown in this chapter. The constitution of the major product is assigned on the basis of the very high field chemical shift of the aromatic H10 proton for the *N*-arylated products (**415**, **417**, and **428**), an nOe analogous to that for **412** for the *N*-alkylated products (**408**, **419**, **421**, **423**, **426**, and **429**–**431**), and an abnormally high-field resonance for the *N*-CH_2 because of shielding by the nearby *p*-carbomethoxyphenyl group in **426**.

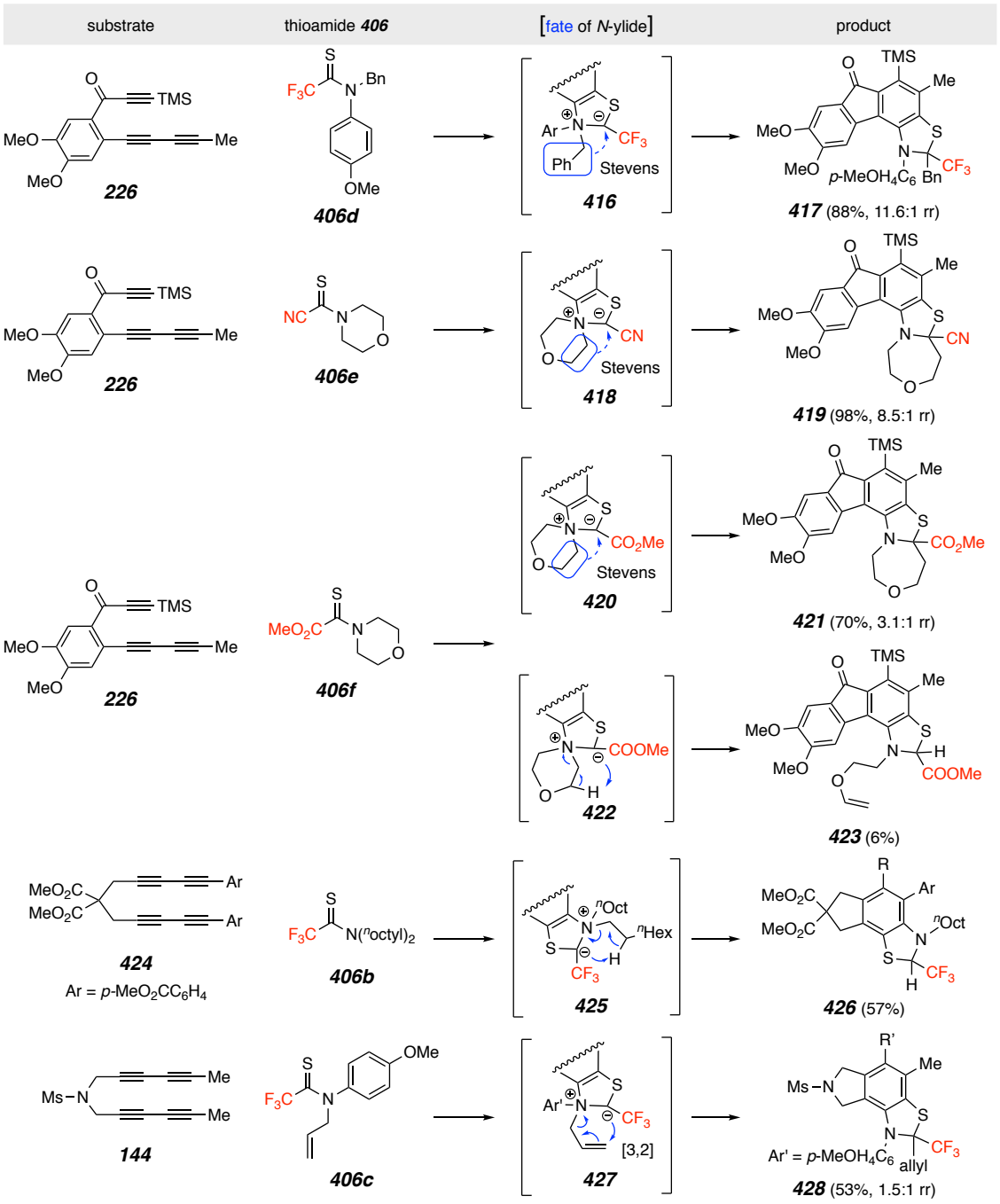

Figure 36. Products arising from several different electron-deficient thioamides **406** and several different benzyne precursors via the mechanistic events suggested in the intermediate ammonium ylides.

Another example of this new type of cycloaddition (Figure 35b) was revealed when the *N*-allyl trifluorothioacetamide **406c** (3 equiv.) was heated (85 °C) with triyne **226**. The dihydrobenzothiazole **415** results from a [3,2]-sigmatropic rearrangement of the allyl group, which again implicates the intermediacy of the ammonium ylide **414b**, formed through capture of **312** by the polarized thioamide **406c**.

We then explored a series of reactions (Figure 36) to probe additional aspects of the reaction.[100,101,102,103] First, would other electron withdrawing groups in the thioamide also promote this new type of cycloaddition reaction? The reactions using thioamides **406d-f**, containing $–CF_3$, –CN, and $–CO_2Me$ groups, respectively, all gave rise to products (**417**, **419**, and **423**, respectively) that demonstrate just that. Also, a minor product **421**, presumably from elimination, was formed in the $–CO_2Me$ case. Second, is the reaction unique to benzyne **226**? No, as evidenced by the conversions of **424** and **144** to products **426** and **428**, respectively, via eliminative or [3,2]-sigmatropic processes within the ammonium ylides **425** or **427**, respectively.

Trapping with the pyrrolidine-containing thioamide **406g** revealed an additional new mode of reaction (Figure 37) beyond the products of Stevens rearrangement (**429**) and elimination (**430**). Here, we also isolated the novel, dihydrobenzo-1,4-thiazine derivative **431**.[104] We suggest that this formally ring expanded compound arises from a C–H insertion event within the intermediate, isomeric carbene **433**, arising from dissociation of the nitrogen atom from the ammonium ylide carbon. This overall process

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[100] Stevens, T. S.; Creighton, E. M.; Gordon, A. B.; MacNicol, M. CCCCXXIII.—Degradation of quaternary ammonium salts. Part I. *J. Chem. Soc.* **1928**, 3193–3197.
[101] Sommelet, M. On a particular mode of intramolecular rearrangement. *Hebd, C. R. Seances Acad. Sci.,* **1937**, *205*, 56.
[102] Vanecko, J. A.; Wan, H.; West, F. G. Recent advances in the Stevens rearrangement of ammonium ylides: application to the synthesis of alkaloid natural products. *Tetrahedron*, **2006**, *62*, 1043–1062.
[103] Clayden, J.; Donnard, M.; Lefranc, J.; Tetlow, D. J. Quaternary centres bearing nitrogen (α-tertiary amines) as products of molecular rearrangements. *Chem. Commun*. **2011**, *47*, 4624–4639.
[104] This compound was obtained as a single diastereomer, but the NCHCHS vicinal coupling constant (4.0 Hz) did not allow for the confident assignment of its relative configuration.

reveals yet another facet of the reactivity of the ammonium ylides encountered in this study. The reverse reaction, generation of an ammonium ylide from a carbene, is known.[105] However, we were unable to further expand this chemistry to other ring systems or chemical environments. We have tried using a thioamide with different *N*-heterocycles (i.e. 4-membered azetidine, and 6-membered piperidine), and neither gave desired 1,4-thiazine. Trapping *in situ* of the carbene **433** was also considered, but not successful.

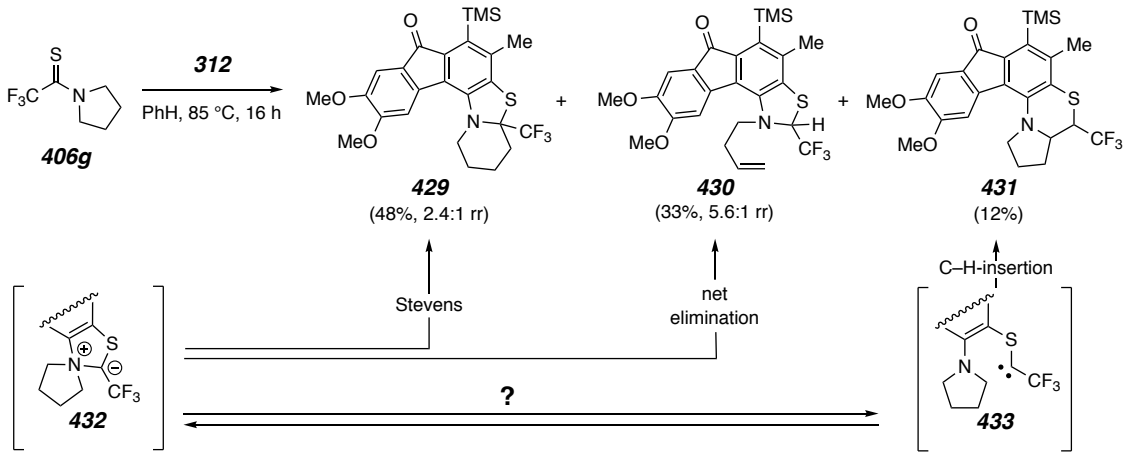

Figure 37. Pyrrolidino thioamide **406g** gave rise to three distinct types of products.

A comment about the observed regioselectivities leading to the major constitutional isomer in these reactions is warranted. In most cases the major product is consistent with the well-established preference for benzyne **312** to add nucleophilic species[39] at the *sp*-hybridized carbon with the larger internal bond angle[11,37]. In contrast, the benzynes derived from **424** and **144** generally show a lower degree of regioselectivity for the addition of nucleophiles. The rr for the product **428** and its isomer is only 1.5:1. However, **426** was formed as the sole dihydrobenzothiazole. This substrate (and

[105] Bamford, W. R.; Stevens, T. S.; Wright, J. W. 829. Degradation of quaternary ammonium salts. Part IX. Attempts to prepare presumed intermediates having co-ordinately linked carbon. *J. Chem. Soc.* **1952**, 4334–4338.

intermediate benzyne), uniquely among all studied here, contains a bulky aryl substituent adjacent to one of the benzyne carbons and thus sterically guides the nucleophilic sulfur atom to add to the distal benzyne carbon. This demonstrates that steric differences encountered during benzyne trapping reactions can override (at least small) inherent electronic preferences.[106]

4.3 Summary

In conclusion, this study of reactions of thioamides bearing an electron withdrawing substituent on the thiocarbonyl carbon (cf. **406**) with benzynes generated by the HDDA reaction of tri- and tetrayne precursors (cf. **226**) has led to the identification of a new type of [3+2]-cycloaddition reaction. The sulfur and nitrogen atoms of the thioamide engage the benzyne *sp*-carbon atoms to produce an intermediate ammonium ylide structure. This species shows a variety of different paths for reaction, including several heretofore unseen, as deduced from the products that are produced. This adds to the overall body of understanding of these relatively rarely encountered species. Overall, this work represents another instance in which the HDDA cycloisomerization reaction has allowed a fundamentally new type of transformation to be discovered.

[106] Medina, J. M.; Mackey, J. L.; Garg, N. K.; Houk, K. N. The Role of Aryne Distortions, Steric Effects, and Charges in Regioselectivities of Aryne Reactions. *J. Am. Chem. Soc.* **2014**, *136*, 15798–15805.

Chapter 5. Divergent Reactivity by Glycidol Analogs: Ring Cleavage *via* Pinacol-like Rearrangements vs. Oxirane Fragmentations

Disclaimer: A large portion of the work presented in this Chapter is adopted from a manuscript published recently in Organic Letters.[107]

5.1 Previous Reports of Benzyne Trapping with Oxygen Nucleophiles

Many oxygen-containing nucleophiles are known to function as nucleophilic reagents that effectively engage classically generated arynes to give aryl ether or ester products (Figure 38). These trapping agents include alcohols,[108] carboxylic acids,[29] and phenols.[59] A previous report has also shown that styrene oxide reacts with *o*-benzyne to yield aryl enol ethers.[109] Selective multi-component reactions in which the benzyne engages, first, a cyclic ether and, then, an alcohol have also been demonstrated.[108]

HDDA-derived benzynes are also known to engage with oxygen nucleophiles. Previous reports from our group showed that alcohols[41] or phenols[57] can react with thermally-generated benzynes in different fashions *via*, namely, dihydrogen transfer (with alcohols) and the phenol-ene process (with phenols). In this chapter, I will demonstrate various hydroxy-containing cyclic ethers (e.g., glycidol derivatives, Figure 38) to trap HDDA-benzynes. These characteristically tend to give rearranged products by way of a pinacol-like rearrangement process in which the cyclic ether ring is cleaved (cf. curved arrows in Figure 38, which indicate the overall bond reorganization). The only related rearrangement reactions of glycidol derivatives that we can find are those induced by silyl triflate reagents, a reaction motif first reported by Jung and coworkers.[110]

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[107] Zhang, J.; Hoye, T. R. Divergent reactivity during the trapping of benzynes by glycidol analogs: Ring cleavage via pinacol-like rearrangements vs. oxirane fragmentations. *Org. Lett.* **2019**, *21*, 2615−2619.
[108] Thangaraj, M.; Bhojgude, S. S.; Mane, M. V.; Biju, A. T. From Insertion to Multicomponent Coupling: Temperature Dependent Reactions of Arynes with Aliphatic Alcohols. *Chem. Commun*. **2016**, *52*, 1665–1668.
[109] Beltran-Rodil, S.; Peña, D.; Guitián, E. Reaction of Benzyne with Styrene Oxide: Insertion of Arynes into a C-O Bond of Epoxides. *Synlett* **2007**, *8*, 1308–1310.
[110] Jung, M. E.; D'amico, D. C. Enantiospecific Synthesis of All Four Diastereomers of 2-Methyl-3-((trialkylsilyl)oxy)alkanals: Facile Preparation of Aldols by Non-Aldol Chemistry. *J. Am. Chem. Soc*. **1993**, *115*, 12208−12209.

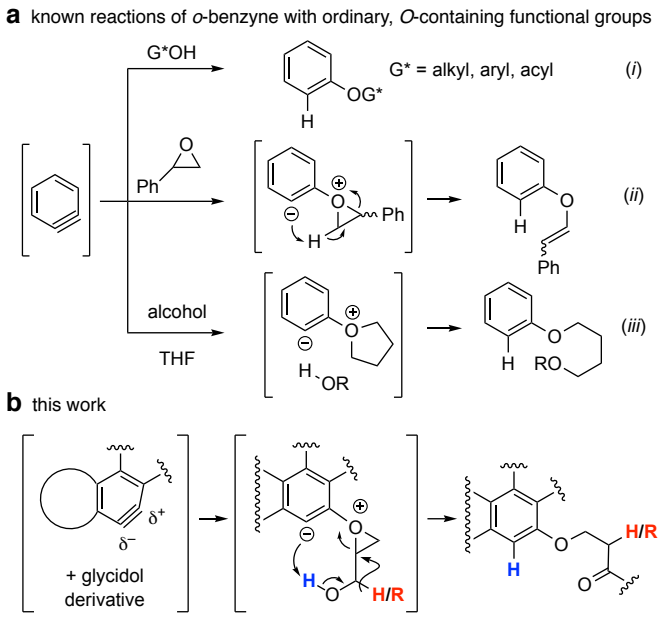


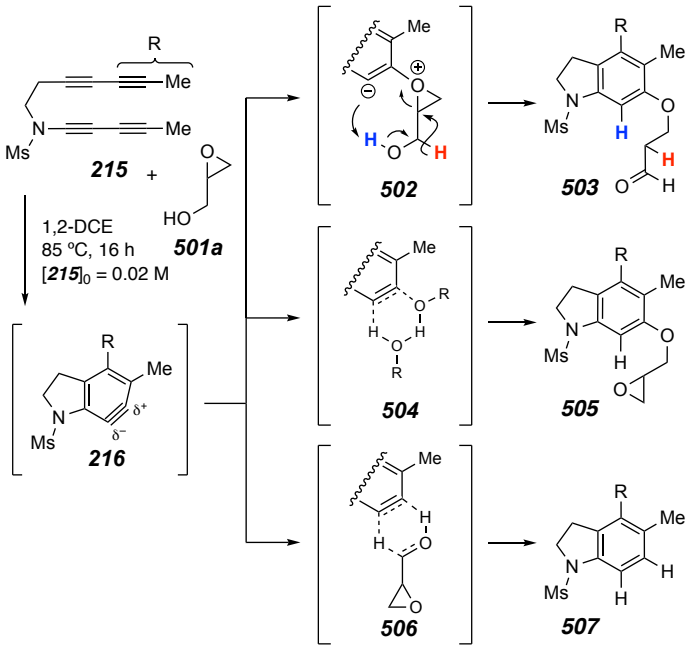
Figure 38. (a) Previous studies of reactions of benzynes with various oxygen-containing nucleophiles. (b) In this report we disclose reactions of hydroxyalkyl substituted cyclic ethers.

5.2 Aryne-induced Semi-pinacol Rearrangement

In 2015, I was interested in a trial reaction performed by one of my lab members. The researcher was trying to trap benzyne **215** with glycidol (**501a**) (Figure 39), but unfortunately, for unknown reasons, the reaction was not successful. I repeated the reaction with the same benzyne **215** and another bottle of glycidol in the inventory, and found that unlike the alcohol addition, this reaction gave a new type of product **503** bearing an aldehyde functional group in 70% yield.

Followed by that early experiment, I explored the simple competition between epoxide and alcohol moieties within the same trapping molecule by generating the HDDA-benzyne **216** (from heating triyne **215**) in the presence of glycidol. Three products were identified: aldehyde **503**, epoxide **505**, and the H_2-addition product **507**.

Each can be rationalized by the events indicated in the bracketed structures labeled **502, 504**, and **506**, respectively.[111]



entry	$[501a]_0$	503	505	507
1	2.0 M	43%	49%	2%
2	0.4 M	66%	23%	2%
3	0.06 M	70%	6%	1%

Figure 39. Competition between epoxide and alcohol moieties using various concentrations.

For all of the reactions reported in this chapter, we only observed a single regioisomer. This outcome is consistent with the extent and direction of the distortion of the benzyne intermediates (cf. **216**, Figure 39)[11,106] as well as the selectivities seen for numerous previously reported examples of nucleophilic trapping reactions of the HDDA polyyne substrates used in this study. The structure of that sole regioisomer was confirmed by a nuclear Overhauser experiment (NOE) for a product from each of **503**, **505** and **507**.

[111] These bracketed depictions are not intended to represent full mechanistic details. For example, the rearrangements could either be concerted or, arguably more likely for stereoelectronic reasons, stepwise, the latter involving an initial proton transfer to produce an intermediate alkoxide-oxonium zwitterion.

The ratio of products **503**, **505** and **507** (Figure 39) was shown to depend on the amount of glycidol that was used. In the case of the highest concentration of that trapping agent (entry 1, 2.0 M, 100 equiv.), the aryl ether **505**, arising from addition of the alcohol hydroxyl in **501a** to the benzyne, predominated slightly over the amount of rearranged aldehyde **503**. A trace of the dihydrogen transfer product **507** was formed.[40,41] On the other hand, the use of only 3 equiv. of **501a** (entry 3, 0.06 M) resulted in a good yield of the aldehyde, again a small amount of **507**, and just 6% of the aryl ether **505**. The varying amount of **505** is consistent with our understanding[41] that the addition of primary alcohols to an HDDA-benzyne likely proceeds by way of the dimer of the alcohol (cf. **504**), the concentration of which is reduced significantly across this range of initial concentrations of **501a**. The formation of the aldehyde **503** can be rationalized by initial 1,3-zwitterion formation from attack of the ether oxygen atom at the more electrophilic benzyne atom (cf. **502**). Intramolecular proton transfer would generate an alkoxide-oxonium ion species within which 1,2-hydride migration ensues. Finally, arene **507** is the result of dihydrogen transfer to the benzyne from the primary hydroxymethyl substituent in **501a**, a process that we have shown to be a concerted event for simple primary alcohols (cf. **506**).[40,41]

To explore the question of whether the strained oxirane ring was necessary to promote this kind of ring-opening/rearrangement reaction, we carried out experiments using 2-(hydroxymethyl)tetrahydrofuran (**501b**, Figure 40, panel a) to trap the benzyne derived from triyne **226**. The major product, **508**, was a linear homolog of the glycidol-derived aldehyde **503**. A small amount of the dihydrogen-trapped product **509** was observed as well. Trapping with 2-(tetrahydropyranyl)methanol (the homolog of **501b**) was briefly examined. Similar product mixtures composed of four principle products were observed (alcohol addition, dihydrogen addition, an unidentified aldehyde, and the aldehyde homolog of **508** unfortunately as the very minor component).

We used a deuterium labeling experiment (Figure 40, panel b) to seek support for the 1,2-hydride shift proposed to account for formation of **508**. Indeed, when **226** was heated in the presence of **501b-*d*$_2$**, in which the carbinol carbon is a CD_2 group, the aldehyde product was primarily labeled at both the aldehydo hydrogen and at one of the hydrogen atoms alpha to the aldehyde (cf. **508-*d*$_2$**). Because the sample of the trapping

agent **501b-*d*$_2$**, produced by $LiAlD_4$ reduction of methyl 2-tetrahydrofuroate, also contained ca. 4% of **501b-*d*$_1$**, small amounts of the isomeric monodeuterated products **508-*d*$_1$** and **508-*d*$_1$'** (Figure 40, panel c) were also detected in the ^{1}H NMR spectrum of the sample of aldehyde **508-*d*$_2$** produced in this experiment. Qualitatively there was a greater amount of **508-*d*$_1$** than **508-*d*$_1$'** formed, as would be expected from a normal kinetic isotope effect associated with the product-determining, 1,2-hydride shift[112,113] Partial overlap of key resonances in the ^{1}H NMR spectrum precluded an accurate, quantitative determination of the actual **508-*d*$_1$** : **508-*d*$_1$'** product ratio.

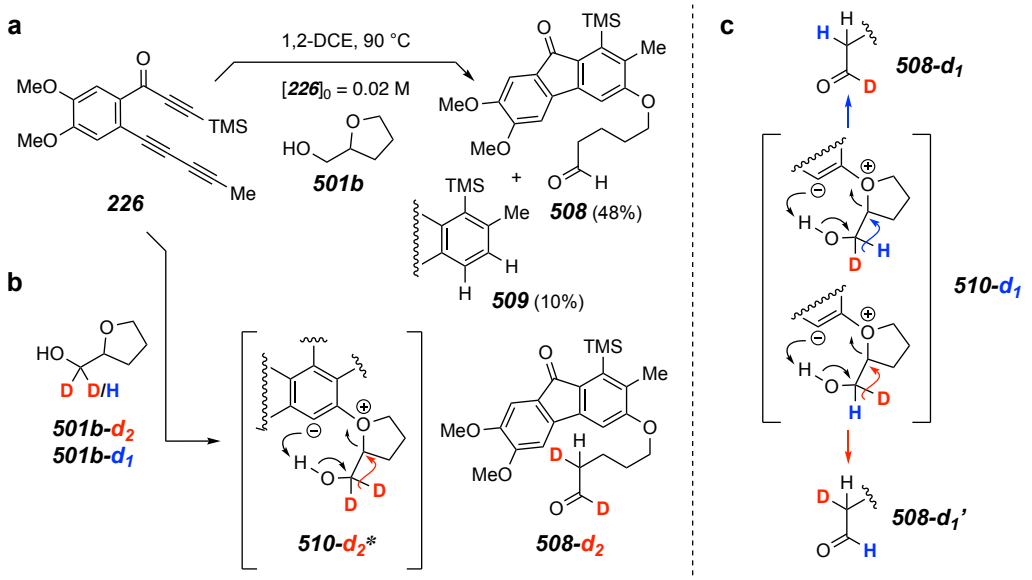


Figure 40. (a) Trapping reactions using a 5-membered cyclic ether. (b) A deuterium-labeling experiment that supports a pinacol-like mechanism. (c) The greater amount of isomeric monodeuterated product **508-*d*$_1$** compared to **508-*d*$_1$'** is consistent with preferential migration of protide vs. deuteride.

[112] Smith, W. B.; Bowman, R. E.; Kmet, T. The Role of Hydrogen in the Pinacol Rearrangement of 2-Methyl-2,3-butanediol. *J. Am. Chem. Soc.* **1959**, *81*, 997–1003.
[113] Smith, W. B. Hydrogen as a Migrating Group in Some Pinacol Rearrangements: a DFT study. *J. Phys. Org. Chem.* **1999**, *12*, 741−746.

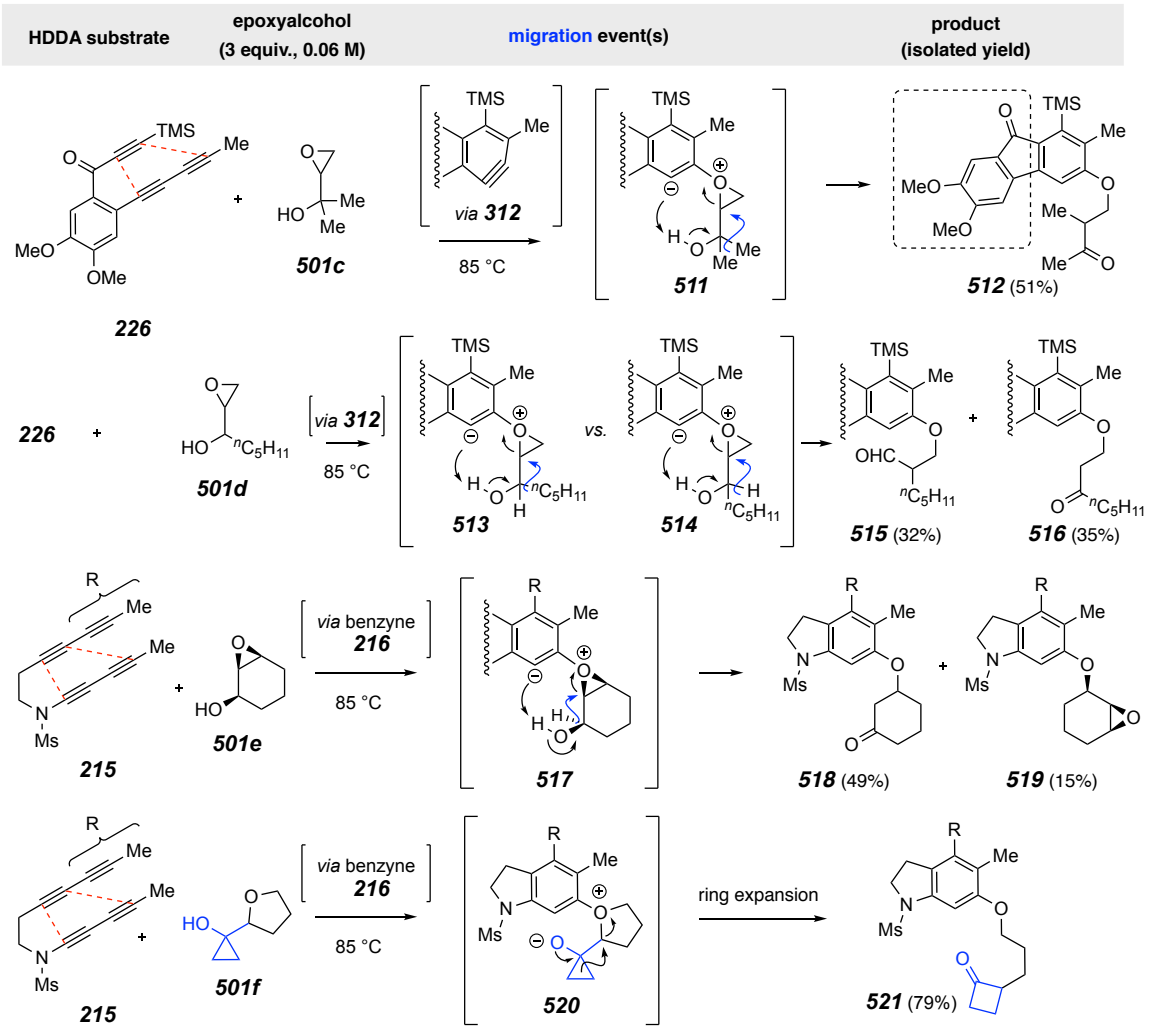


Figure 41. Trapping of HDDA-derived benzynes from **226** or **215** by epoxide-containing substrates **501c**–**501f**: Pinacol-like rearrangements.

We then probed the reactivity of the additional epoxide-containing substrates **501c**–**501i**. Those shown in Figure 41 (**501c**–**501f**) proceeded with 1,2-pinacol-like migration of an alkyl group or a hydride. Dimethyl substituted glycidol **501c** gave rise to methyl migration product **512**. In the case of **501d**, these two pathways were in competition (cf. **513** vs. **514**). However, stereoelectronic factors are in play, as suggested by the fact that the more constrained *cis*-epoxycyclohexanol **501d** rearranged (to **516**) only with hydride migration, presumably because the endocyclic C–C bond is not well-oriented for overlap with the activated epoxide C–O bond. (cf. **515**). Trapping benzyne **216** (generated from

tetrayne **215**) with cyclohexene oxide derivative **501e** resulted in a mixture of two products, with the semi-pinacol product **518** as the major product. We also designed a substrate that contains a cyclopropane ring, namely, 1-(tetrahydrofuran-2-yl)55yclopropane-1-ol (**501f**). The reaction between **501f** and benzyne **216** cleanly yielded the ring-expanded cyclobutanone derivative **521**, by releasing the ring strain.

5.3 Oxirane Fragmentations

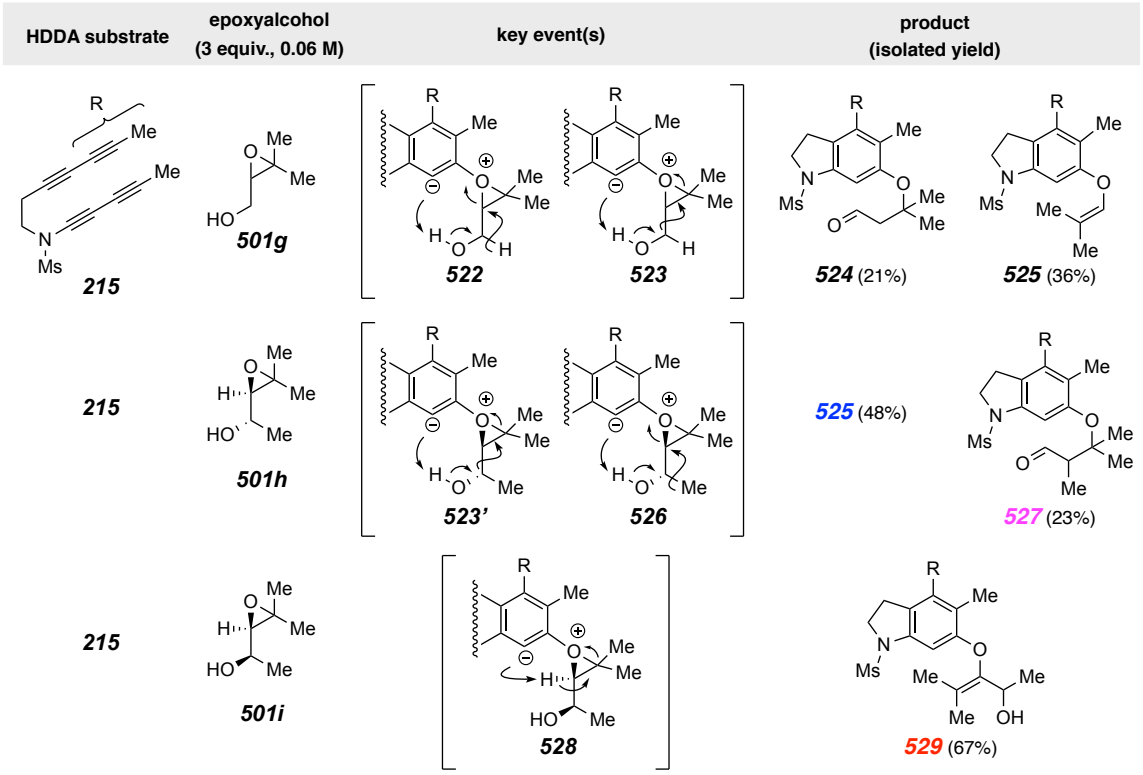


Figure 42. Trapping (85 °C) of HDDA-derived benzynes from **215** by epoxide substrates **501g**–**501i**: Rearrangement vs. fragmentation.

Different reactivity patterns were revealed using the tri-substituted epoxides **501g–I** (Figure 42), each of which gave rise to epoxide-fragmentation products. One mode of fragmentation involves C–C bond cleavage to liberate either formaldehyde (from **523**) or acetaldehyde (from **523'**). The acetaldehyde byproduct formed in the reaction of **501h** was observed in nearly equimolar amount to that of **525** when the reaction of **215** and **501h** was performed in $CDCl_3$ and assayed directly by ^1H NMR spectroscopy. However,

the diastereomer **501i** gave neither a pinacol-like product nor the fragmentation product **525**. Instead, it followed a new reaction course, yielding the enol ether **529** as the only isolated product.

These differing fates of diastereomers **501h** and **501i** are instructive and serve to reinforce the importance of stereoelectronic factors in the reactivity of these benzyne-derived internal ion pairs (Figure 43). The dominant conformation for each of these tri-substituted epoxyalcohols (and the initial zwitterions derived therefrom) can be expected to have the carbinol methine proton oriented toward the *cis*-methyl group. Consequentially, the blue hydroxyl proton is more readily accessible to the aryl carbanion in **523'** than in **528**. In the case of **501h**, fragmentation (to **525**) and 1,2-methyl migration (to **527**, magenta arrows in **526**) compete. Alternatively, the blue hydroxyl proton in diastereomer **501i** is remote from the carbanion center, allowing abstraction of the epoxide methine proton to intervene, leading to the enol ether **529** (red arrows).

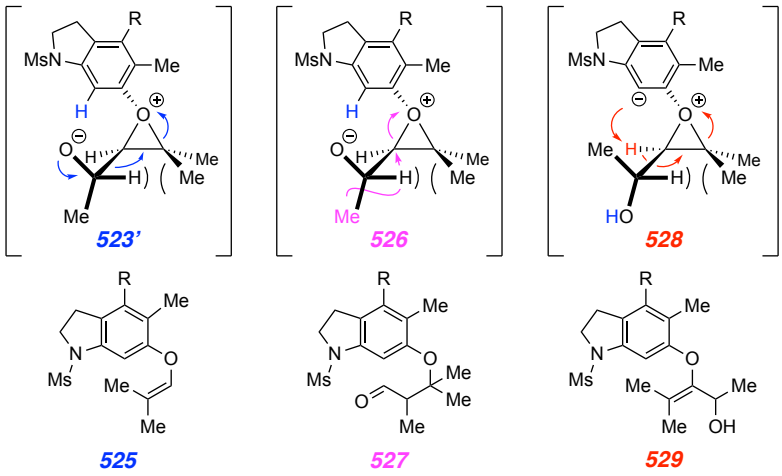


Figure 43. Fate of the zwitterions generated by trapping benzyne with **501g–501i**.

To complement the experiments already described, we have carried out several "one-off" experiments, which are portrayed in Figure 44. As mentioned, the reaction of styrene oxide with 1,2-dehydrobenzene[109] has been previously studied as one of only a few reports we have found describing oxirane-aryne reactivity. Similar to those previous

reports[114,115], the reaction of **226** with styrene oxide yielded two isomeric aryl enol ethers—namely, **533** and **534**, along with the dihydrobenzofuran derivative **535** (Figure 44, panel a). The formation of these three products can be rationalized via the events depicted in **530**–**532**. Alternatively, the reaction of tetrayne **215** with cyclohexene oxide gave **539**–**541** (Figure 44, panel b). The first and last proceeded by processes (**539** and **541**) analogous to the styrene oxide reaction and the third, **540**, by an eliminative opening[116] via **537**. The *cis*-ring-fusion in **541** was assigned on the basis of a modest 6.5 Hz coupling constant between H_{6a} and H_{10a}.[117,118] This outcome requires net retention of configuration at the site of epoxide cleavage, which suggests the intermediacy of a zwitterion like that in **538**.

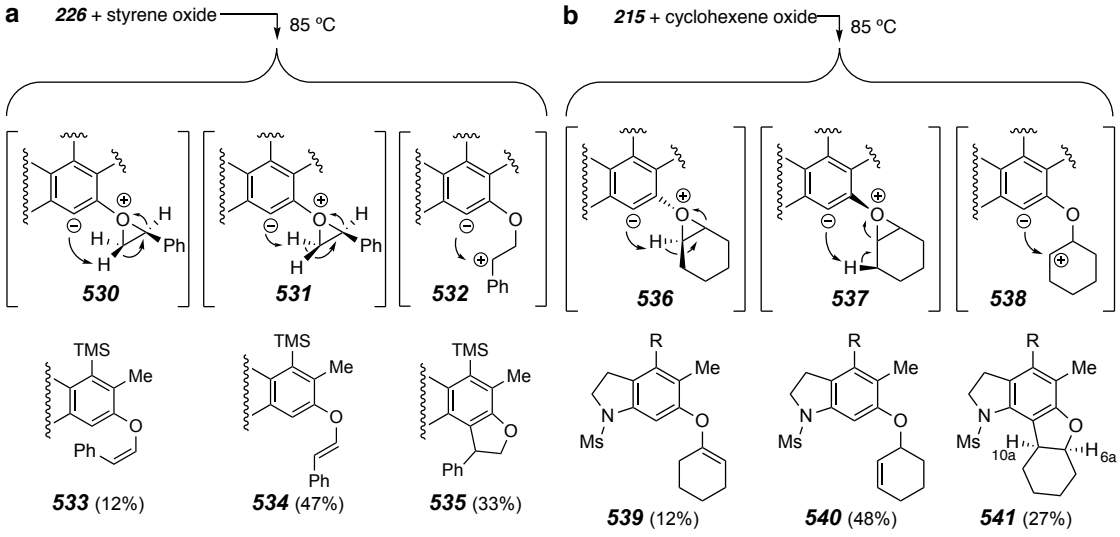


Figure 44. Reactions between HDDA-derived benzynes and simple epoxides.

[114] Okuma, K.; Hino, H.; Sou, A.; Nagahora, N.; Shioji, K. Cascade Approach to Trichloroalkyl Phenyl Ethers from Benzyne, Epoxides, and Chloroform. *Chem. Lett.* **2009**, *38*, 1030–1031.

[115] Okuma, K.; Fukuzaki, Y.; Nojima, A.; Sou, A.; Hino, H.; Matsunaga, N.; Nagahora, N.; Shioji, K.; Yokomori, Y. Three Component Reaction of Arynes with Cyclic Ethers and Active Methines: Synthesis of □-Trichloroalkyl Phenyl Ethers. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 1238–1247.

[116] Sdergren, M. J.; Andersson, P. G. New and Highly Enantioselective Catalysts for the Rearrangement of *meso*-Epoxides into Chiral Allylic Alcohols. *J. Am. Chem. Soc*. **1998**, *120*, 10760–10761.

[117] A similar *trans*-fused tetrahydrodibenzofuran derivative showed an 11.6 or 12.8 Hz coupling: Zhao, G.; Wang, B.; Yang, W.; Ren, H. Lewis-Acid-Promoted Arylation Reaction: Synthesis of Dihydrobenzofuran Derivatives from Aryltriazenes. *Eur. J. Org. Chem.* **2012**, 6236–6247.

[118] A somewhat similar *cis*-fused tetrahydrodibenzofuran derivative showed an 8.4 Hz coupling: Yamashita, M.; Yadav, N. D.; Sawaki, T.; Takao, I.; Kawasaki, I.; Sugimoto, Y.; Miyatake, A.; Murai, K.; Takahara, A.; Kurume, A.; Ohta, S. Asymmetric Total Synthesis of (−)-Linderol A. *J. Org. Chem.* **2007**, *72*, 5697–5703.

5.4 Summary and Future Prospects

In conclusion, we have described here a variety of reactions between benzynes and cyclic ethers that bear adjacent hydroxyalkyl substituents. Because the benzynes are produced thermally, these reactions take place in the absence of other reagents or byproducts of the benzyne-generating event. Many of the reactions can be rationalized as proceeding through preferential attack of the cyclic ether oxygen to form a 1,3-zwitterion, followed by internal proton transfer and subsequent opening of the cyclic oxonium ion. An isotopic labeling experiment established that 1,2-hydride migration within the alkoxy-oxonium intermediate is most likely operative. Studies of a number of substituted glycidol derivatives, including a diastereomeric pair, reveal a variety of different reaction pathways that are rationalized on stereoelectronic grounds. Reaction outcomes using the simple epoxides styrene oxide and cyclohexene oxide demonstrate the viability of some of the elementary steps used to rationalize the reaction outcomes with the hydroxyalkyl epoxides. A cyclopropane ring expansion reaction results in the formation of a novel cyclobutanone.

Chapter 6. Total Synthesis of Isohericerin

Disclaimer: A portion of the work presented in this Chapter is largely adopted from a manuscript in preparation.

6.1 Previous Syntheses of Isohericerin

Isohericerin (**601**) is a geranyl resorcylate natural product isolated from edible mushroom *Hericium erinaceus*. It has been widely used in traditional Chinese medicine for the treatment of dyspepsia, gastric ulcer, and enervation.[119] It belongs to the subfamily of resorcylate natural products (Figure 45) that consist of an isoindolinone core and a geranyl side chain; some of these show significant biological activities including antioxidant,[120] antitumor,[121] antimicrobial[122] activities.

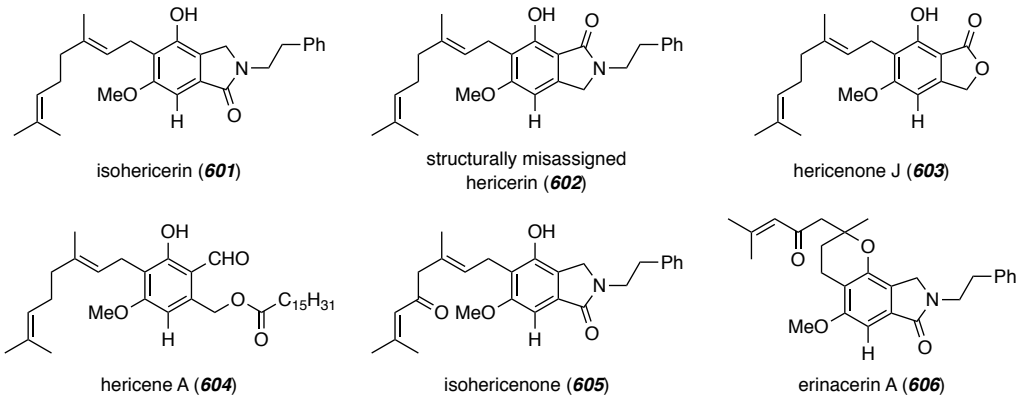


Figure 45. The family of resorcylate natural products.

Isohericerin was first isolated by Tsuneda and co-workers in 1991,[123] but the original assigned structure (i.e., **602**) was subsequently shown to be incorrect. In 2012 the

[119] Ma, B.-J.; Shen, J.-W.; Yu, H.-Y.; Ruan, Y.; Wu, T.-T.; Zhao, X. Hericenones and Erinacines: Stimulators of Nerve Growth Factor (NGF) Biosynthesis in *Hericium Erinaceus*. *Mycology* **2010**, *1*, 92−98.
[120] Hui, X.; Pin-Ru, W.; Zheng-Yu, S.; Xiang-Dong, C. Chemical Analysis of *Hericium Erinaceum* Polysaccharides and Effect of the Polysaccharides on Derma Antioxidant Enzymes, MMP-1 and TIMP-1 Activities. *Int. J. Biol. Macromol*. **2010**, 47, 33–36.
[121] Mizuno, T. Bioactive Substances in *Hericium erinaceus* (Bull.: Fr.) Pers. (Yamabushitake), and Its Medicinal Utilization. *Int. J. Med. Mushrooms* **1999**, *1*, 105–119.
[122] Dong-Myong, K.; Chul-Woo, P.; Han-Gyu, K.; Won-Mok, P. *Mycology* **2000**, *28*, 33–38.
[123] Kimura, Y.; Nishibe, M.; Nakajima, H.; Hamasaki, T.; Shimada, A.; Tsuneda, A.; Shigematsu, N. Hericerin, a New Pollen Growth Inhibitor from the Mushroom *Hericium Erinaceum*. *Agric. Biol. Chem*. **1991**, *55*, 2673–2674.

corrected structure (i.e., **601**) was established through the synthesis efforts of Kobayashi and co-workers.[124] Other members of this family of secondary metabolites were synthesized utilizing a $CuBr_2$-mediated tandem cyclization, which was employed first in synthesizing hericenone J (**603**) and hericene A (**604**)[125] and then, in isohericerin. In 2013, Miranda *et al.* carried out a concise total synthesis utilizing a Claisen rearrangement followed by a Pd and Cu-catalyzed lactamization to construct the isoindolinone core. The resulting 5-step total synthesis yielded isohericerin in 34% overall yield.[126] More recently, Lee and co-workers synthesized isohericerin *via* a Pd-catalyzed cross coupling between a bromoarene and geranyl boronate in 44% overall yield.[127] They also developed a copper-catalyzed methylboronation to further synthesize isohericenone (**605**) and erinacerin (**606**).

Hexadehydro-Diels–Alder (HDDA) reaction[29] has recently become a rapidly growing area in the field of aryne chemistry.[39] It has been demonstrated to be useful for synthesizing multi-functionalized arene derivatives in excellent regio- and chemoselectivity. So far there are only a few total syntheses reported using HDDA-cycloisomerization to construct the key ring system.[53,54] We have been interested in applying an HDDA strategy in total synthesis, and herein we reported a concise total synthesis of isohericerin using HDDA reaction.

6.2 Retrosynthetic Analysis

The retrosynthetic plan is depicted in Figure 46. The key event was a methanol trapping reaction of the benzyne (**607**), which was to be generated by an HDDA-cycloisomerization of the tethered triyne **608**. A Tamao-Kumada oxidation of an arylsilane would install the phenolic OH in **601**. The triyne precursor **608** could be

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[124] Kobayashi, S.; Inoue, T.; Ando, A.; Tamanoi, H.; Ryu, I.; Masuyama, A. Total Synthesis and Structural Revision of Hericerin. *J. Org. Chem*. **2012**, *77*, 5819–5822.
[125] Kobayashi, S.; Ando, A.; Kuroda, H.; Ejima, S.; Masuyama, A.; Ryu, I. Rapid Access to 6-Bromo-5,7-dihydroxyphthalide 5-Methyl Ether by a $CuBr_2$-Mediated Multi-Step Reaction: Concise Total Syntheses of Hericenone J and 5'-Deoxohericenone C (Hericene A). *Tetrahedron* **2011**, *67*, 9087–9092.
[126] Gómez-Prado, R. A.; Miranda, L. D. Concise Total Synthesis of Hericerin Natural Product. *Tetrahedron Lett*. **2013**, *54*, 2131–2132.
[127] Mun, B.; Kim, S.; Yoon, H.; Kim, K. H.; Lee, Y. Total Synthesis of Isohericerin, Isohericenone, and Erinacerin A: Development of a Copper-Catalyzed Methylboronation of Terminal Alkynes. *J. Org. Chem*. **2017**, *82*, 6349−6357.

assembled from building blocks **612**–**614**, using a Cu-catalyzed Cadiot–Chodkiewicz cross coupling to create the necessary conjugated diyne moiety. Amide **611** could be prepared from commercially available phenylethylamine (**613**) and propiolic acid (**614**), and bromoalkyne **610** could be synthesized from commercially available geranyl bromide (**612**) in 2 steps.

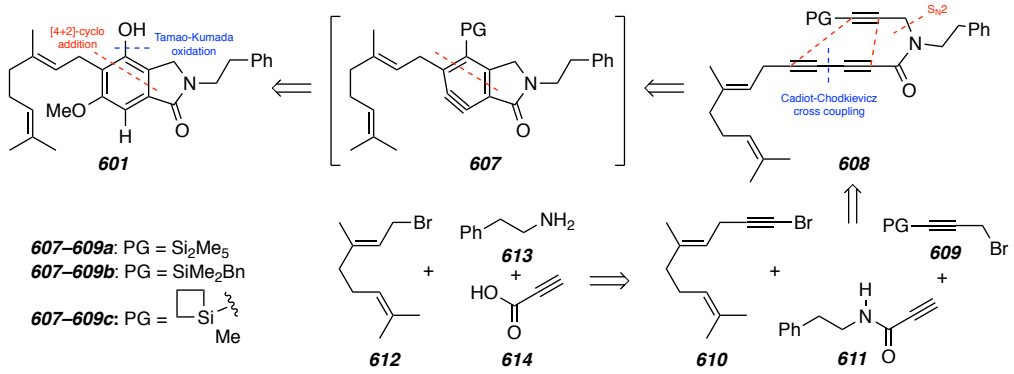

Figure 46. Retrosynthetic analysis of isohericerin.

6.3 Total Synthesis of Isohericerin

We first turned to DFT calculations to explore the regioselectivity of the benzyne **607** envisioned in our key step (Figure 47). Distortion of unsymmetrical benzynes has been shown to be a reliable method for forecasting and rationalizing the regioselectivity of benzyne trapping events.[11,106] The benzyne *sp*-hybridized carbon atom with the larger internal bond angle is presumed to have greater *p*-character in its associated in-plane π-bond and, hence, to be the site with greater electrophilicity. The computed [M06-2X/6-311+G(d,p), SMD:methanol] distortion angles of benzyne **615**, a slightly simplified

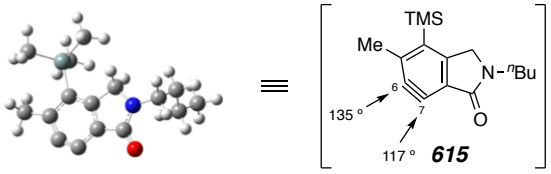

Figure 47. Computational study of the geometry and benzyne distortion angle of the model benzyne **615**.

version of **607**, were 135° (at C6) and 117° (at C7). This suggested not only that the mode of addition of the nucleophilic methanol oxygen should prefer the desired attack at C6 but also that the level of that selectivity should be high.

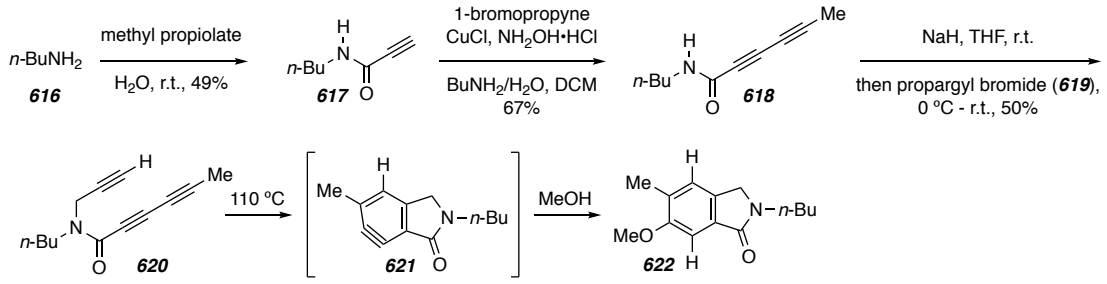

Figure 48. Synthesis of the model compound **622**.

Following the DFT study, we designed a simple model compound **622** for synthetic analysis. Shown in Figure 48 is the synthesis of the model compound **622**. Propiolamide **617** was synthesized from *n*-butylamine (**616**) and methyl propiolate in 49% yield. The amide was then coupled with 1-bromopropyne to give diyne **618**, and was propargylated to give rise to triyne precursor **620**. Finally, triyne **620** was heated in methanol at 110 ºC to give the model compound **622**, presumably via distorted benzyne **621**. The regioisomerism of isoindolone **622** was confirmed by ^{1}H NMR and 1D nOe analysis.

We then proceeded to the first trial of the total synthesis. To begin with, bromoalkyne **610** was obtained from geranyl bromide in two steps (Figure 49). The first step involves a displacement of bromide by ethynyl Grignard reagent, and subsequent bromination of the terminal alkyne gave the bromoalkyne **610** in 95% yield over two steps. Next, compound **609a** was synthesized from propargyl bromide (**619**) in 19% yield. Meanwhile, we synthesized *N*-phenylethylpropiolamide (**611**) in 60% yield using EDCI coupling between phenylethylamine and propiolic acid. Next, we performed a Cadiot–Chodkiewicz cross coupling between propiolamide **611** and bromoalkyne **610**, giving diyne **624** in 48% yield. However, the reaction to propargylate the free N–H group was not successful. We have examined multiple deprotonation conditions and various bases and all of the reactions gave complex mixture or turned to oligomerized material. We then redesigned our synthetic route and constructed the diyne **623a** in our first step. Propargylation of the propiolamide **611** gave the desired diyne **623a** only in 17% yield,

and it was then subject to Cadiot–Chodkiewicz coupling with bromoalkyne **610** to give the triyne precursor **608a** in 71% yield.

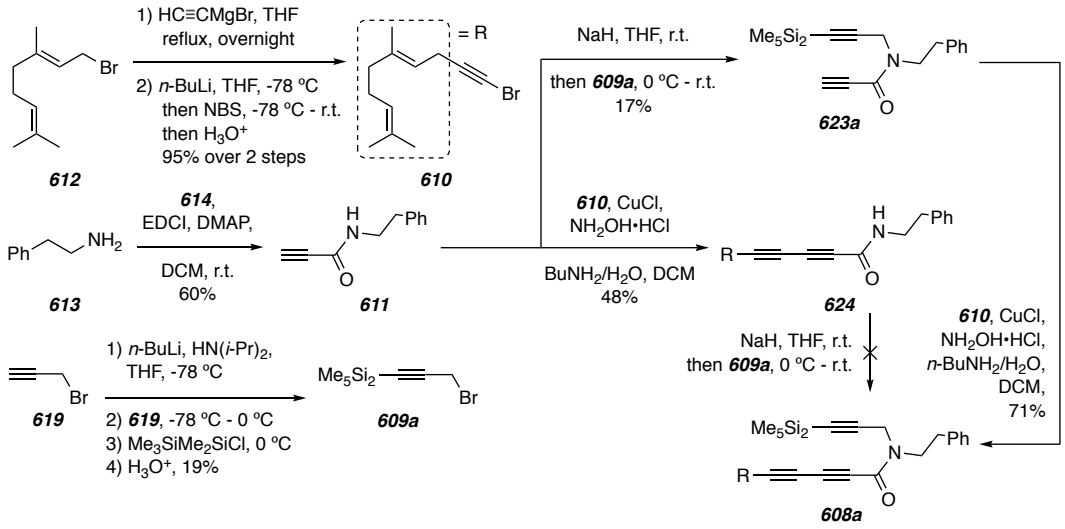

Figure 49. The first trial of the total synthesis.

The final stage of this total synthesis was shown in Figure 50. With triyne **608a** in hand, we performed the key HDDA cycloisomerization step. After heating triyne **608a** at 110 ºC in methanol, we obtained the isoindolinone **625a** as predicted. The regioisomerism was observed between the aryl proton and the methoxy group, and between the methoxy group and the benzyl methylene (cf. **625a**, Figure 50). Unfortunately, the subsequent Tamao–Kumada oxidation was not successful. We have screened a few deprotection conditions, using TBAF or KF, but either resulted in completely desilylation, or no reaction. Change of the oxidizing agent from hydrogen peroxide to various peracid gave rise to epoxidation on the geranyl moiety.

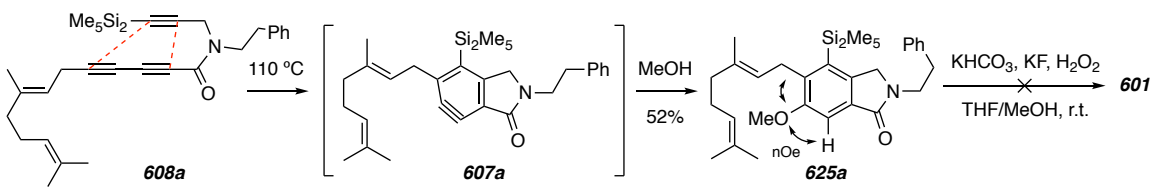

Figure 50. Unsuccessful final stage of the total synthesis.

We switched the silyl protecting group from disilane to benzyldimethylsilane and methylsiletane and repeated the synthesis (Figure 51). Because the first silylation on the propargyl bromide (**619**) was low yielding using LDA, we improved the synthesis with direct deprotonation of **619** with *n*-BuLi at -78 ºC and then silylation on the terminal alkyne. The lithium halogen exchange seemed to be slower than the deprotonation under -78 ºC, and the yield was doubled this time (66%). We then performed the similar synthesis (cf. Figure 49) to give diyne **623b** and then triyne precursor **608b**. Heating triyne **608b** in methanol gave the HDDA product **625b** with desired regioisomerism in 71% yield. However, the Tamao–Kumada oxidation was still not successful and we ran out of materials at this moment.

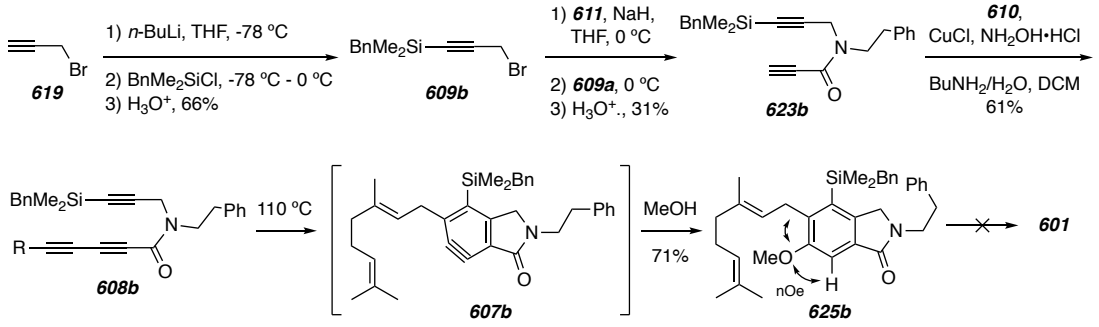

Figure 51. Second trial of the total synthesis by changing the silyl protecting group.

6.4 Summary

In conclusion, we have developed a new synthetic approach towards the natural product isohericerin. The core arene ring was built via the hexadehydro-Diels–Alder cycloisomerization. Cadiot–Chodkiewicz coupling and propargylation of the amide were employed to build the triyne precursor. For future prospect of this total synthesis, one could consider the silacyclobutane protecting group (i.e., **607**–**609c**, Figure 46) developed by Denmark *et al*.[128,129] as an alternative in the final Tamao–Kumada oxidation step. Synthesis of the propargyl bromide derivative **609c** can be done by an *in situ* generation

[128] Denmark, S. E.; Griedel, B. D.; Coe, D. M. The chemistry of enoxysilacyclobutanes: highly selective, uncatalyzed aldol additions. *J. Org. Chem*. **1993**, *58*, 988−990.
[129] Denmark, S. E.; Griedel, B. D.; Coe, D. M.; Schnute, M. E. Chemistry of Enoxysilacyclobutanes: Highly Selective Uncatalyzed Aldol Additions. *J. Am. Chem. Soc*. **1994**, *116*, 7026−7043.

of the chlorosilane followed by silylation of the lithium acetylide. The next most problematic step of this synthesis is the propargylation of the amide **611**, which could potentially be improved by using a different base (e.g., *n*-BuLi, Na, or KHMDS). Various ways of disconnection of the target molecule could also be considered.

Supplementary Information for Chapter 2

General Experimental Information

^{1}H and ^{13}C NMR spectra were measured on Bruker Avance 500 or 400 spectrometers at 500 or 400 MHz, respectively. ^{1}H NMR chemical shifts for spectra in $CDCl_3$ are referenced to TMS (δ 0.00 ppm). Non-first order multiplets in ^{1}H NMR spectra are identified as such by the designation "nfom". The following format is used for reporting resonances: the chemical shift in ppm [multiplicity, coupling constant(s) (Hz), integral, and assignment]. ^{1}H NMR assignments are designated by the neighboring atoms, e.g., C*Ha*Hb. Analysis of coupling constant was guided by methods we have reported earlier.[130,131] ^{13}C NMR chemical shifts for spectra recorded in $CDCl_3$ are referenced to the carbon in $CDCl_3$ (δ 77.16 ppm).

Infrared spectra were measured on a Midac Corporation (Prospect 4000) FT-IR spectrometer in the attenuated total reflectance (ATR) mode on a germanium window. Samples were neat thin films.

High-resolution mass spectrometry (HRMS) measurements were recorded in the electrospray ionization mode (ESI) on a Bruker BioTOF II (ESI-TOF) instrument. PEG was used as an added internal standard/calibrant. Samples were introduced to the instrument as solutions in methanol. HRMS data were collected as several separate measurements during each of several successive injections. The median value from a total of eleven separate values is reported for each compound.

Melting points were taken on a Köfler hot-stage or a Barnstead Mel-Temp 3.0 apparatus and are uncalibrated.

MPLC refers to medium pressure liquid chromatography (25-200 psi) using dry-packed columns of silica gel (25-35 μm, 60 Å pore size). A Waters HPLC pump (M6000) was used to provide flow rates of ca. 6 mL•min^{-1}, A Waters R401 differential refractive index detector and a Gilson 116 UV detector were used to monitor the contents of the eluent. Flash chromatography was carried out on E. Merck silica gel (230-400 mesh). Thin layer

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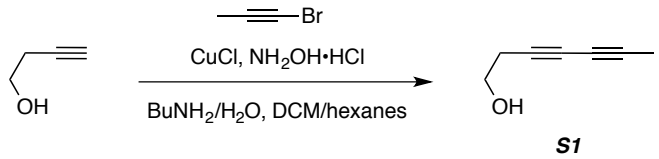
[130] Hoye, T. R.; Hanson, P. R.; Vyvyan, J. R. A Practical Guide to First-Order Multiplet Analysis in ^{1}H NMR Spectroscopy. *J. Org. Chem*. **1994**, *59*, 4096-4103.

[131] Hoye, T. R.; Zhao, H. A Method for Easily Determining Coupling Constant Values: An Addendum to "A Practical Guide to First-Order Multiplet Analysis in ^{1}H NMR Spectroscopy". *J. Org. Chem*. **2002**, *67*, 4014–4016.

chromatography was carried out on plastic-backed plates of silica gel. These were visualized by UV detection and, then, a solution of basic potassium permanganate. Reported reaction temperatures are those of the temperature of the external heating or cooling bath that was used. HDDA reactions were routinely performed in a threaded vial or culture tube fitted with an inert, Teflon®-lined cap.

GC-MS data were collected on an Agilent 5975 MSD outfitted with a 6890 GC. A 30 m x 0.25 mm ID, HP-5 column was used; the He flow rate was 1 mL• min^{-1}. The temperature program was: 50 ºC/1.5 min, 20 ºC min^{-1} to 250 ºC).

Hepta-3,5-diyn-1-ol (S1)



S1

Cuprous chloride (1.49 g, 15.0 mmol) and hydroxylamine hydrochloride (6.95 g, 100 mmol) were added to a one-liter, three-necked, round-bottomed flask equipped with a magnetic stirrer bar. The reaction vessel was purged with nitrogen and then a degassed solution of $BuNH_2/H_2O$ (40 mL amine and 60 mL water) and dichloromethane (DCM, 200 mL) were added. The colorless mixture was cooled to 0 ºC. In the meantime, a solution of 3-butyn-1-ol (7.01 g, 100 mmol) in DCM (100 mL) was prepared, and 15 mL of this butynol solution was placed in an addition funnel and added in a dropwise fashion into the reaction mixture under N_2. The remaining 85 mL of the butynol solution and degassed 1-bromopropyne in hexanes (1.47 M, 100 mL) were then placed into the addition funnel and this solution was added over 30 min. The reaction mixture was allowed to warm to room temperature, and the progress was monitored by TLC (1:1 hexanes:EtOAc). The reaction was quenched by the addition of saturated NH_4Cl solution (200 mL), and the aqueous layer was extracted twice with DCM (50 mL each). The combined organic layer was washed with saturated NH_4Cl solution (100 mL) and brine (100 mL), dried with $MgSO_4$, filtered, and concentrated. The resulting residue was purified by passage through a silica gel plug (1:1 hexanes:EtOAc) to give alcohol **S1** as a colorless oil (10.6 g, 97.7%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.74 (q, *J* = 6.2 Hz, 2H, C*H*$_2$OH), 2.52 (tq, *J* = 6.2, 1.0 Hz, 2H, OCH$_2$C*H*$_2$), 1.91 (t, *J* = 1.0 Hz, 3H, C*H*$_3$), and 1.76 (br s, 1H, O*H*).

^{13}C NMR (125 MHz, $CDCl_3$): δ 73.9, 73.1, 67.2, 64.2, 60.9, 23.6, and 4.1.

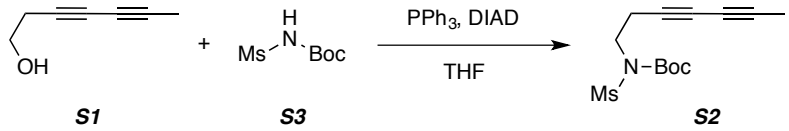
IR (neat): 3341, 2954, 2919, 2893, 2843, 2264, 1424, 1377, 1333, 1278, 1240, 1188, 1045, 990, 877, and 844 cm^{-1}.

GC-MS: t_R = 4.233 min, [*m/z* (ion, rel int)]: 108 (M^+, 100), 78 (M^+–CH_2O, 85), and 77 (M^+–CH_2OH, 75).

TLC: R_f 0.5 (1:1 hexanes:EtOAc)

mp: solidifies upon storage in a -20 ºC freezer.

***tert*-Butyl hepta-3,5-diyn-1-yl(methylsulfonyl)carbamate (S2)**



To a stirred solution of alcohol **S1** (10.5 g, 97.2 mmol) and carbamate **S3** (20.8 g, 106.7 mmol) in THF (300 mL) was added PPh_3 (30.6 g, 116.7 mmol). The solution was cooled to 0 ºC and DIAD (23.0 mL, 116.7 mmol) was added dropwise over 20 min. The reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was then concentrated and filtered through Celite. The filtrate was diluted with diethyl ether (100 mL), washed with water (50 mL) and brine (50 mL), dried with $MgSO_4$, and concentrated. The resulting residue was purified by flash chromatography (11:1, then 3:1 hexanes:EtOAc) to give carbamate **S2** as a white solid (25.1 g, 90.3%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.90 (t, J = 6.8 Hz, 2H, NCH_2), 3.36 (s, 3H, O_2SCH_3), 2.63 (tq, J = 6.8, 1 Hz, 2H, NCH_2CH_2), 1.92 (t, J = 1.0 Hz, 3H, ≡CCH_3), and 1.58 (s, 9H, $C(CH_3)_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 151.2, 84.9, 74.2, 72.4, 67.6, 64.2, 44.1, 42.4, 28.0, 20.1, and 4.2.

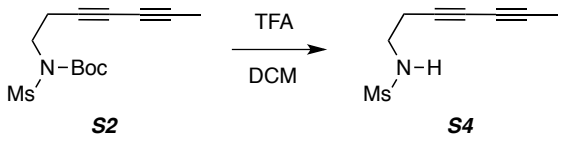
IR (neat): 2980, 2940, 2922, 2264, 1729, 1352, 1276, 1260, 1139, 1087, 964, 909, and 842 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{13}H_{19}NNaO_4S^+$ [M+Na^+] 308.0933, found 308.0935.

TLC: R_f 0.15 (3:1 hexanes:EtOAc)

mp: 47-51 °C.

***N*-(Hepta-3,5-diyn-1-yl)methanesulfonamide (S4)**



S2 ***S4***

Carbamate **S2** (24.8 g, 86.7 mmol) was dissolved in DCM (300 mL) and cooled to 0 ºC. TFA (32.3 mL, 434.3 mmol) was added dropwise over 20 min. The reaction mixture was allowed to warm to room temperature and stirred for 4 h, and then quenched by the addition of saturated $NaHCO_3$ solution (200 mL). The mixture was separated and the organic layer was washed with saturated $NaHCO_3$ solution (100 mL) and brine (100 mL), dried with $MgSO_4$, and concentrated. The residue was purified by recrystallization (DCM/hexanes) and filtered to give sulfonamide **S4** as a white crystalline solid (11.8 g). The filtrate was concentrated and purified by flash chromatography (1:1 hexanes:EtOAc) to give an additional portion of sulfonamide **S4** as a white solid (2.80 g). The combined yield (14.6 g, 90.8%, 97.4% b.r.s.m.).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.52 (br s, 1H, N*H*), 3.30 (dt, *J* = 6.4, 6.4 Hz, 2H, NCH_2), 3.00 (s, 3H, O_2SCH_3), 2.56 (t, *J* = 6.3 Hz, 2H, NCH_2CH_2), and 1.92 (s, 3H, ≡CCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 74.6, 72.1, 68.0, 63.9, 41.7, 41.1, 21.3 and 4.2.

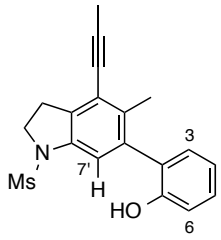
IR (neat): 3237, 3017, 2936, 2913, 2876, 2846, 2206, 2152, 2043, 1446, 1299, 1134, 1071, 980, and 781 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_8H_{11}NNaO_2S^+$ $[M+Na]^+$ requires 208.0403; found 208.0401.

TLC: R_f 0.25 (1:1 hexanes:EtOAc).

mp: 102-105 °C.

2-(5-Methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)phenol (217a)



A solution of sulfonamide **215** (40.0 mg, 0.162 mmol) and phenol (23.0 mg, 0.242 mmol) in 1,2-dichloroethane (8 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (3:1 hexanes:EtOAc) to give phenol **217a** (25.9 mg, 46.9%) as a white amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (ddd, *J* = 7.5, 1.6, 1.6 Hz, 1H, Ar*H5*), 7.20 (s, 1H, Ar*H7′*), 7.06 (dd, *J* = 7.4, 1.5 Hz, 1H, Ar*H3*), 6.98–6.93 (m, 2H, Ar*H6* and Ar*H4*), 4.82 (s, 1H, O*H*), 4.00 (t, *J* = 8.5 Hz, 2H, NCH_2), 3.22 (app td, *J* = 8.5, 2.2 Hz, 2H, NCH_2CH_2), 2.86 (s, 3H, O_2SCH_3), 2.18 (s, 3H, ArCH_3), and 2.14 (s, 3H, ≡CCH_3).

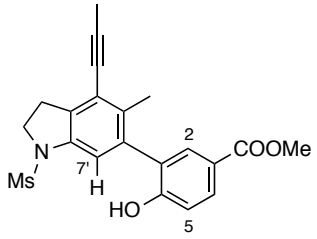
^{13}C NMR (125 MHz, $CDCl_3$): δ 152.4, 139.9, 135.9, 134.2, 134.2, 130.2, 129.3, 127.6, 122.5, 120.6, 115.4, 114.5, 94.9, 75.9, 50.4, 34.6, 28.3, 17.5, and 4.6.

IR (neat): 3480, 3012, 2954, 2917, 2855, 2228, 1590, 1491, 1462, 1416, 1341, 1243, 1188, 1147, and 983 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{19}H_{19}NNaO_3S^+$ [M+Na^+] 364.0983, found 364.0983.

TLC: R_f 0.2 (3:1 hexanes:EtOAc).

Methyl 4-hydroxy-3-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)benzoate (217b)



A solution of sulfonamide **215** (40.0 mg, 0.162 mmol) and methyl *p*-hydroxybenzoate (36.9 mg, 0.242 mmol) in 1,2-dichloroethane (8 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (2:1 hexanes:EtOAc) to give compound **217b** (13.3 mg, 20.6%) as an amorphous white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (dd, *J* = 8.7, 2.3 Hz, 1H, Ar*H6*), 7.80 (d, *J* = 2.2 Hz, 1H, Ar*H2*), 7.18 (s, 1H, Ar*H7′*), 6.99 (d, *J* = 8.7 Hz, 1H, Ar*H5*), 5.28 (s, 1H, O*H*), 4.08–3.97 (m, 2H, NCH_2), 3.88 (s, 3H, OCH_3), 3.27–3.21 (m, 2H, NCH_2CH_2), 2.88 (s, 3H, O_2SCH_3), 2.15 (s, 3H, ArCH_3), and 2.14 (s, 3H, ≡CCH_3).

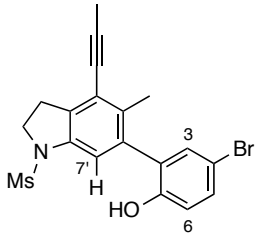
^{13}C NMR (125 MHz, $CDCl_3$): δ 166.8, 156.7, 140.1, 134.7, 134.6, 134.2, 132.2, 131.4, 127.6, 122.8, 122.7, 115.5, 114.4, 95.2, 75.8, 52.0, 50.3, 34.7, 28.3, 17.4, and 4.6.

IR (neat): 3402, 3015, 2953, 2922, 2855, 2225, 1714, 1605, 1505, 1436, 1345, 1276, 1244, 1158, 1114, 1014, and 969 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{21}H_{21}NNaO_5S^+$ $[M+Na^+]$ 422.1038, found 422.1038.

TLC: R_f 0.15 (2:1 hexanes:EtOAc).

4-Bromo-2-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)phenol (217c)



A solution of sulfonamide **215** (40.0 mg, 0.162 mmol) and 4-bromophenol (41.9 mg, 0.242 mmol) in 1,2-dichloroethane (8 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (2:1 hexanes:EtOAc) to give phenol **217c** (24.9 mg, 36.7%) as an amorphous white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (dd, *J* = 8.7, 2.5 Hz, 1H, Ar*H5*), 7.19 (d, *J* = 2.5 Hz, 1H, Ar*H3*), 7.16 (s, 1H, Ar*H7′*), 6.85 (d, *J* = 8.7 Hz, 1H, Ar*H6*), 4.67 (s, 1H, O*H*), 4.07–3.98 (m, 2H, NCH_2), 3.27–3.19 (m, 2H, NCH_2CH_2), 2.89 (s, 3H, O_2SCH_3), 2.17 (s, 3H, $ArCH_3$), and 2.14 (s, 3H, ≡CCH_3).

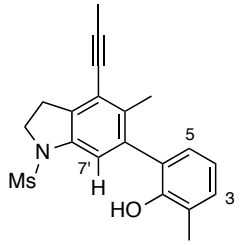
^{13}C NMR (125 MHz, $CDCl_3$): δ 151.7, 140.1, 134.8, 134.3, 134.1, 132.6, 132.2, 129.5, 122.8, 117.2, 114.2, 112.5, 95.3, 75.7, 50.2, 34.8, 28.3, 17.4, and 4.6.

IR (neat): 3477, 3018, 2960, 2918, 2855, 2232, 1591, 1483, 1459, 1399, 1341, 1271, 1186, 1156, 1147, 1116, and 966 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{19}H_{18}{}^{79}BrNNaO_3S^+$ [$M+Na^+$] 442.0088, found 442.0092.

TLC: R_f 0.2 (2:1 hexanes:EtOAc).

2-Methyl-6-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)phenol (217d)



A solution of sulfonamide **215** (40.0 mg, 0.162 mmol) and *o*-cresol (26.2 mg, 0.242 mmol) in 1,2-dichloroethane (8 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (2:1 hexanes:EtOAc) to give phenol **217d** (33.0 mg, 57.4%) as a white solid. Analysis of the crude product mixture (^{1}H NMR) suggested that a [4+2] Diels-Alder adduct analogous to **223**$_{[4+2]}$ (see manuscript) was present to the extent of 6%. This adduct eluted with an essentially identical R_f as that of **217d** and is evident (^{1}H NMR) as a minor contaminant in the chromatographed sample of **217d**.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (s, 1H, Ar*H7′*), 7.13 (dd, *J* = 7.2, 1.5 Hz, 1H, Ar*H3*), 6.89 (dd, *J* = 7.8, 2.0 Hz, 1H, Ar*H5*), 6.86 (dd, *J* = 7.3, 7.3 Hz, 1H, Ar*H4*), 4.66 (s, 1H, O*H*), 4.02 (app td, *J* = 8.4, 1.6 Hz, 2H, NCH_2), 3.23 (app td, *J* = 8.6, 1.7 Hz, 2H, NCH_2CH_2), 2.87 (s, 3H, O_2SCH_3), 2.29 (s, 3H, Ar^1CH_3), 2.17 (s, 3H, Ar^2CH_3), and 2.14 (s, 3H, ≡CCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 150.5, 140.0, 136.0, 134.3, 134.2, 130.6, 127.6, 127.0, 124.3, 122.6, 120.0, 114.6, 94.9, 75.9, 50.3, 34.6, 28.3, 17.5, 16.1, and 4.6.

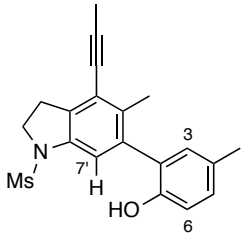
IR (neat): 3466, 3011, 2917, 2855, 2225, 1591, 1489, 1463, 1418, 1345, 1325, 1233, 1158, and 967 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{20}H_{21}NNaO_3S^+$ [M+Na$^+$] 378.1140, found 378.1144.

TLC: R_f 0.2 (2:1 hexanes:EtOAc).

mp (mixture): 241 °C (with decomp).

4-Methyl-2-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)phenol (217e)



A solution of sulfonamide **215** (40.0 mg, 0.162 mmol) and *p*-cresol (26.2 mg, 0.242 mmol) in 1,2-dichloroethane (8 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (3:1 hexanes:EtOAc) to give phenol **217e** (35.2 mg, 61.2%) as a white amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (s, 1H, Ar*H7'*), 7.07 (dd, *J* = 8.1, 2.1 Hz, 1H, Ar*H5*), 6.86 (d, *J* = 2.1 Hz, 1H, Ar*H3*), 6.84 (d, *J* = 8.1 Hz, 1H, Ar*H6*), 4.51 (s, 1H, O*H*), 4.01 (app td, *J* = 8.5, 2.3 Hz, 2H, NCH_2), 3.23 (app td, *J* = 8.5, 2.2 Hz, 2H, NCH_2CH_2), 2.87 (s, 3H, O_2SCH_3), 2.30 (s, 3H, C4CH_3), 2.19 (s, 3H, C5'C*H3*), and 2.14 (s, 3H, ≡CCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 150.1, 139.9, 136.1, 134.2, 134.1, 130.6, 129.8, 127.3, 122.5, 120.6, 115.1, 114.6, 94.8, 76.0, 50.4, 34.6, 28.3, 20.5, 17.5, and 4.6.

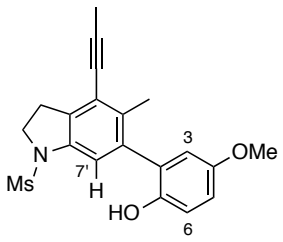
IR (neat): 3484, 3015, 2920, 2859, 2229, 1590, 1505, 1471, 1458, 1342, 1278, 1151, and 989 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{20}H_{21}NNaO_3S^+$ [M+Na^+] 378.1140, found 378.1145.

TLC: R_f 0.15 (3:1 hexanes:EtOAc).

mp: solid turned to crystalline at ca. 190 ºC and then 225 °C (with decomp).

4-Methoxy-2-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)phenol (217f)



A solution of sulfonamide **215** (40.0 mg, 0.162 mmol) and *p*-methoxyphenol (30.1 mg, 0.242 mmol) in 1,2-dichloroethane (8 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (3:1 hexanes:EtOAc) to give phenol **217f** (42.6 mg, 70.9%) as a white amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (s, 1H, Ar*H7′*), 6.88 (d, *J* = 8.8 Hz, 1H, Ar*H6*), 6.83 (dd, *J* = 8.9, 2.9 Hz, 1H, Ar*H5*), 6.62 (d, *J* = 2.9 Hz, 1H, Ar*H3*), 4.40 (s, 1H, O*H*), 4.01 (t, *J* = 8.5 Hz, 2H, NCH_2), 3.77 (s, 3H, OCH_3), 3.23 (br app td, *J* = 8.5, 2.1 Hz, 2H, NCH_2CH_2), 2.87 (s, 3H, O_2SCH_3), 2.19 (s, 3H, ArCH_3), and 2.14 (s, 3H, ≡CCH_3).

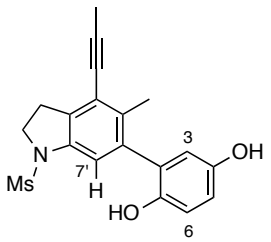
^{13}C NMR (125 MHz, $CDCl_3$): δ 153.4, 146.4, 139.9, 135.9, 134.2, 134.1, 128.2, 122.6, 116.1, 115.3, 114.6, 114.4, 94.9, 75.9, 55.8, 50.3, 34.7, 28.3, 17.4, and 4.6.

IR (neat): 3484, 3006, 2954, 2922, 2835, 2235, 1595, 1502, 1467, 1418, 1341, 1275, 1207, 1154, 1114, 1038, 991, and 968 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{20}H_{21}NNaO_4S^+$ [M+Na^+] 394.1089, found 394.1096.

TLC: R_f 0.15 (3:1 hexanes:EtOAc).

2-(5-Methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)benzene-1,4-diol (217g)



A solution of sulfonamide **215** (40.0 mg, 0.162 mmol) and hydroquinone (26.7 mg, 0.242 mmol) in 1,2-dichloroethane (8 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (1:1 hexanes:EtOAc) to give benzenediol **217g** (38.2 mg, 66.1%) as an amorphous white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (s, 1H, Ar*H7′*), 6.83 (d, *J* = 8.7 Hz, 1H, Ar*H6*), 6.76 (dd, *J* = 8.7, 3.0 Hz, 1H, Ar*H5*), 6.57 (d, *J* = 3.0 Hz, 1H, Ar*H3*), 4.42 (s, 1H, O*H*), 4.32 (s, 1H, O*H*), 4.02 (t, *J* = 8.6 Hz, 2H, NCH_2), 3.23 (app td, *J* = 8.5, 3.1 Hz, 2H, NCH_2CH_2), 2.88 (s, 3H, O_2SCH_3), 2.19 (s, 3H, ArCH_3), and 2.14 (s, 3H, ≡CCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 151.6, 149.0, 146.5, 140.0, 134.3, 134.0, 128.3, 122.6, 116.7, 116.2, 116.1, 114.4, 95.0, 75.9, 50.3, 34.7, 28.3, 17.4, and 4.6.

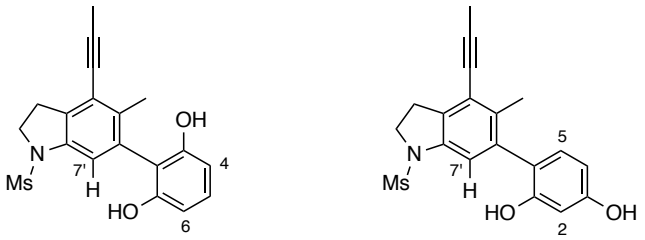
IR (neat): 3446, 3015, 2963, 2919, 2229, 1588, 1506, 1446, 1417, 1338, 1196, 1154, 1097, and 969 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{19}H_{19}NNaO_4S^+$ $[M+Na^+]$ 380.0933, found 380.0940.

TLC: R_f 0.25 (1:1 hexanes:EtOAc).

2-(5-Methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)benzene-1,3-diol (217i) and

4-(5-Methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)benzene-1,3-diol (217h)



A solution of sulfonamide **215** (40.0 mg, 0.162 mmol) and resorcinol (53.4 mg, 0.485 mmol) in 1,2-dichloroethane (8 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (2:1 hexanes:EtOAc) to give, in order of elution, benzenediol **217i** (8.3 mg, 14.4%) as an amorphous white solid and **217h** (30.3 mg, 52.5%) as an amorphous light yellow solid.

Data for 217i

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (s, 1H, Ar*H7′*), 7.15 (t, *J* = 8.2 Hz, 1H, Ar*H5*), 6.56 (d, *J* = 8.2 Hz, 2H, Ar*H4* and Ar*H6*), 4.63 (s, 2H, O*H*), 4.02 (t, *J* = 8.6 Hz, 2H, NCH_2), 3.24 (t, *J* = 8.6 Hz, 2H, NCH_2CH_2), 2.88 (s, 3H, O_2SCH_3), 2.18 (s, 3H, $ArCH_3$), and 2.15 (s, 3H, $\equiv CCH_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 153.3, 140.7, 135.9, 135.4, 129.7, 129.6, 123.5, 115.0, 114.6, 107.6, 95.6, 75.7, 50.3, 34.9, 28.3, 17.1, and 4.6.

IR (neat): 3440, 3009, 2921, 2852, 2232, 1592, 1461, 1339, 1275, 1262, 1152, 1110, 1063, 1006, and 980 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{19}H_{19}NNaO_4S^+$ $[M+Na^+]$ 380.0933, found 380.0941.

TLC: R_f 0.2 (2:1 hexanes:EtOAc).

Data for 217h

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (s, 1H, Ar*H7′*), 6.89 (nfom, 1H, Ar*H5*), 6.46 (s, 1H, Ar*H2*) 6.47-6.43 (nfom, 1H, Ar*H6*), 5.64 (br s, 1H, O*H*), 5.00 (br s, 1H, O*H*), 4.00 (t, *J* = 8.5 Hz, 2H, NCH_2), 3.21 (app td, *J* = 8.5, 1.8 Hz, 2H, NCH_2CH_2), 2.87 (s, 3H, O_2SCH_3), 2.18 (s, 3H, $ArCH_3$), and 2.13 (s, 3H, $\equiv CCH_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.8, 153.4, 139.9, 135.8, 134.7, 134.0, 131.0, 122.5, 120.3, 115.0, 107.9, 102.6, 94.8, 76.0, 50.4, 34.7, 28.3, 17.5, and 4.6.

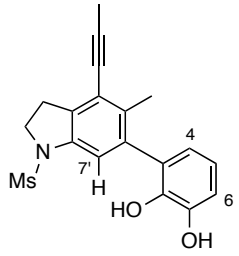
IR (neat): 3428, 3015, 2960, 2925, 2849, 2229, 1595, 1520, 1456, 1333, 1241, 1155, 1104, 1057, and 972 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{19}H_{19}NNaO_4S^+$ [M+Na^+] 380.0933, found 380.0935.

TLC: R_f 0.1 (2:1 hexanes:EtOAc).

mp: heating turned the solid to crystalline material at ca. 135 ºC; then 198 °C (decomp).

3-(5-Methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)benzene-1,2-diol (217j)



A solution of sulfonamide **215** (40.0 mg, 0.162 mmol) and catechol (26.7 mg, 0.242 mmol) in 1,2-dichloroethane (8 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (2:1 hexanes:EtOAc) to give benzenediol **217j** (46.4 mg, 80.2%) as an amorphous white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (s, 1H, Ar*H7′*), 6.92 (dd, *J* = 8.1, 1.5 Hz, 1H, Ar*H4*), 6.85 (dd, *J* = 8.0, 8.0 Hz, 1H, Ar*H*5), 6.63 (dd, *J* = 7.7, 1.5 Hz, 1H, Ar*H6*), 5.35 (s, 1H, O*H*), 4.80 (s, 1H, O*H*), 4.05-3.97 (m, 2H, NCH_2), 3.26-3.20 (m, 2H, NCH_2CH_2), 2.88 (s, 3H, O_2SCH_3), 2.19 (s, 3H, $ArCH_3$), and 2.14 (s, 3H, $\equiv CCH_3$).

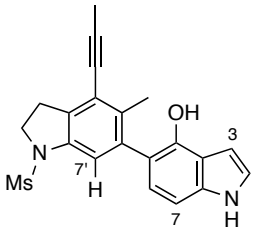
^{13}C NMR (125 MHz, $CDCl_3$): δ 143.9, 140.0, 139.9, 135.5, 134.2, 134.1, 127.9, 122.6, 121.7, 120.8, 114.8, 114.3, 94.9, 75.9, 50.3, 34.7, 28.3, 17.5, and 4.6.

IR (neat): 3475, 2957, 2922, 2852, 2232, 1592, 1474, 1457, 1415, 1330, 1247, 1201, 1143, 1112, 1064, 977, 889, and 828 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{19}H_{19}NNaO_4S^+$ $[M+Na^+]$ 380.0933, found 380.0937.

TLC: R_f 0.15 (2:1 hexanes:EtOAc).

5-(5-Methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-1*H*-indol-4-ol (217k)



A solution of sulfonamide **215** (40.0 mg, 0.162 mmol) and 4-hydroxyindole (32.3 mg, 0.242 mmol) in 1,2-dichloroethane (8 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (2:1 hexanes:EtOAc) to give compound **217k** (31.0 mg, 50.4%) as a light yellow amorphous foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (br s, 1H, N*H*), 7.27 (s, 1H, Ar*H7'*), 7.18 (dd, *J* = 2.7, 2.7 Hz, 1H, Ar*H2*), 7.02 (dd, *J* = 8.3, 0.8 Hz, 1H, Ar*H7*), 6.87 (d, *J* = 8.3 Hz, 1H, Ar*H6*), 6.66 (ddd, *J* = 3.1, 2.2, 0.9 Hz, 1H, Ar*H3*), 4.96 (s, 1H, O*H*), 4.01 (app td, *J* = 8.6, 3.9 Hz, 2H, NCH_2), 3.25 (t, *J* = 8.5, Hz, 2H, NCH_2CH_2), 2.86 (s, 3H, O_2SCH_3), 2.21 (s, 3H, $ArCH_3$), and 2.14 (s, 3H, ≡CCH_3).

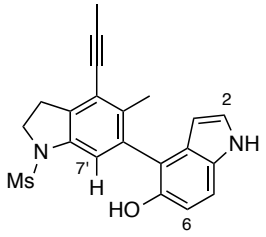
^{13}C NMR (125 MHz, $CDCl_3$): δ 145.3, 139.9, 137.4, 136.8, 134.9, 133.8, 124.4, 123.4, 122.4, 117.2, 116.7, 115.4, 103.9, 99.7, 94.6, 76.2, 50.4, 34.6, 28.4, 17.7, and 4.6.

IR (neat): 3412, 3012, 2960, 2919, 2852, 2230, 1586, 1486, 1457, 1417, 1340, 1265, 1225, 1155, 1110, 1077, 1051, and 968 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{21}H_{20}N_2NaO_3S^+$ [$M+Na^+$] 403.1092, found 403.1097.

TLC: R_f 0.3 (1:1 hexanes:EtOAc).

4-(5-Methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)-1*H*-indol-5-ol (217l)



A solution of sulfonamide **215** (40.0 mg, 0.162 mmol) and 5-hydroxyindole (32.3 mg, 0.242 mmol) in 1,2-dichloroethane (8 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (2:1 hexanes:EtOAc) to give compound **217l** (41.6 mg, 67.6%) as a light yellow amorphous foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (br s, 1H, N*H*), 7.30 (s, 1H, Ar*H7'*), 7.28 (d, *J* = 8.7, 0.9 Hz, 1H, Ar*H7*), 7.10 (dd, *J* = 2.7, 2.7 Hz, 1H, Ar*H2*), 6.88 (d, *J* = 8.7 Hz, 1H, Ar*H6*), 5.99 (ddd, *J* = 3.0, 2.2, 0.9 Hz, 1H, Ar*H3*), 4.55 (br s, 1H, O*H*), 4.02 (t, *J* = 8.5 Hz, 2H, NCH_2), 3.25 (app td, *J* = 8.3, 4.6 Hz, 2H, NCH_2CH_2), 2.84 (s, 3H, O_2SCH_3), 2.16 (s, 3H, ArCH_3), and 2.14 (s, 3H, ≡CCH_3).

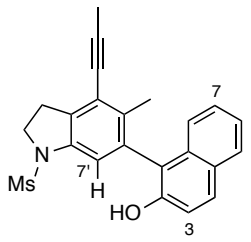
^{13}C NMR (125 MHz, $CDCl_3$): δ 146.0, 140.0, 135.0, 134.5, 134.1, 130.7, 128.0, 125.2, 122.7, 117.2, 115.1, 111.6, 111.4, 101.4, 94.8, 76.1, 50.5, 34.5, 28.3, 17.4, and 4.6.

IR (neat): 3412, 3009, 2960, 2920, 2858, 2228, 1588, 1505, 1440, 1405, 1339, 1241, 1155, 1116, 1081, 1056, and 969 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{21}H_{20}N_2NaO_3S^+$ [M+Na^+] 403.1092, found 403.1101.

TLC: R_f 0.25 (1:1 hexanes:EtOAc).

1-(5-Methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)naphthalen-2-ol (217m)



A solution of sulfonamide **215** (40.0 mg, 0.162 mmol) and 2-naphthol (35.0 mg, 0.242 mmol) in 1,2-dichloroethane (8 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (2:1 hexanes:EtOAc) to give compound **217m** (58.4 mg, 89.3%) as an amorphous white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.9 Hz, 1H, H4), 7.81 (nfom, 1H, H5), 7.34–7.29 (m, 2H, *H6* and *H7*), 7.24 (d, *J* = 8.9 Hz, 1H, *H3*), 7.22 (s, 1H, *H7′*), 7.15 (nfom, 1H, *H8*), 5.04 (s, 1H, O*H*), 4.07 (ddd, *J* = 10.4, 9.5, 7.6 Hz, 1H, NCH_aH_b), 4.04 (ddd, *J* = 10.4, 9.4, 8.2 Hz, 1H, NCH_aH_b) 3.30 (ddd, *J* = 16.8, 9.3, 7.2 Hz, 2H, $NCH_2CH_aH_b$), 3.28 (ddd, *J* = 16.8, 9.6, 7.6 Hz, 2H, $NCH_2CH_aH_b$), 2.85 (s, 3H, O_2SCH_3), 2.14 (s, 3H, $ArCH_3$), and 2.05 (s, 3H, $\equiv CCH_3$).

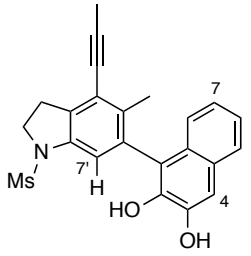
^{13}C NMR (125 MHz, $CDCl_3$): δ 150.1, 140.4, 135.7, 134.7, 133.3, 133.0, 129.6, 128.9, 128.2, 126.7, 124.2, 123.3, 123.0, 120.0, 117.4, 115.3, 95.1, 75.9, 50.4, 34.5, 28.4, 17.2, and 4.6.

IR (neat): 3466, 3012, 2963, 2918, 2232, 1621, 1596, 1513, 1458, 1416, 1344, 1268, 1189, 1157, 1080, 1060, and 968 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{23}H_{21}NNaO_3S^+$ $[M+Na^+]$ 414.1140, found 414.1147.

TLC: R_f 0.2 (2:1 hexanes:EtOAc).

1-(5-Methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)naphthalene-2,3-diol (217n)



A solution of sulfonamide **215** (40.0 mg, 0.162 mmol) and 2,3-naphthalenediol (38.8 mg, 0.242 mmol) in 1,2-dichloroethane (8 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (2:1 hexanes:EtOAc) to give compound **217n** (57.3 mg, 87.0%) as an amorphous pale yellow foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.0 Hz, 1H, Ar*H5*), 7.32 (s, 1H, Ar*H4*), 7.31 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H, Ar*H6* or Ar*H7*), 7.21 (s, 1H, Ar*H7′*), 7.19 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H, Ar*H6* or Ar*H7*), 7.08 (br d, *J* = 8.4 Hz, 1H, Ar*H8*), 5.69 (br s, 1H, O*H*), 5.10 (br s, 1H, O*H*), 4.10 (nfom, 1H, NCH_aH$_b$), 4.03 (nfom, 1H, NCH$_a$$H_b$), 3.36–3.23 (nfom, 2H, NCH_2CH_2), 2.87 (s, 3H, O_2SCH_3), 2.15 (s, 3H, $ArCH_3$), and 2.05 (s, 3H, ≡CCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 144.2, 140.4, 140.3, 135.5, 134.8, 132.8, 129.7, 127.8, 126.9, 124.22, 124.21 123.1, 120.9, 114.9, 110.0, 95.3, 75.8, 50.4, 34.7, 28.4, 17.3, and 4.6.

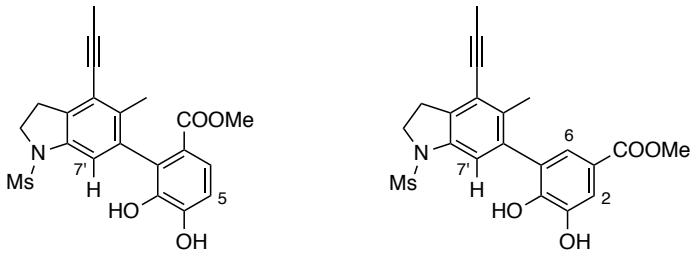
IR (neat): 3440, 3009, 2954, 2919, 2852, 2232, 1517, 1461, 1345, 1264, 1235, 1159, 1109, 1069, and 969 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{23}H_{21}NNaO_4S^+$ [M+Na^+] 430.1089, found 430.1093.

TLC: R_f 0.15 (2:1 hexanes:EtOAc).

Methyl 3,4-dihydroxy-2-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)benzoate (217o) and

Methyl 3,4-dihydroxy-5-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)benzoate (217p)



A solution of sulfonamide **215** (40.0 mg, 0.162 mmol) and methyl 3,4-dihydroxybenzoate (40.8 mg, 0.242 mmol) in 1,2-dichloroethane (8 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (2:1 hexanes:EtOAc) to give, in order of elution, esters **217o** (40.3 mg, 60.0%) and **217p** (10.9 mg, 16.2%), each as a white solid.

Data for 217o

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.6 Hz, 1H, Ar*H6*), 7.08 (s, 1H, Ar*H7′*), 6.94 (d, *J* = 8.6 Hz, 1H, Ar*H5*), 6.14 (s, 1H, O*H*), 5.05 (s, 1H, O*H*), 4.10 (nfom, 1H, NCH_aH_b), 3.92 (nfom, nfom, 1H, $NCH_a\mathit{H_b}$), 3.63 (s, 3H, OCH_3), 3.31–3.16 (nfom, 2H, NCH_2CH_2), 2.84 (s, 3H, O_2SCH_3), 2.12 (s, 3H, $ArCH_3$), and 2.07 (s, 3H, $\equiv CCH_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.2, 147.9, 140.1, 139.9, 134.4, 134.1, 133.8, 128.9, 124.7, 122.6, 121.2, 114.1, 113.8, 94.9, 51.6, 50.4, 34.1, 28.3, 17.1, and 4.5 (this isomer was only sparingly soluble in $CDCl_3$; the resonance for the second alkyne carbon, normally appearing at ca. 75 ppm, was not observed in this spectrum).

IR (neat): 3387, 3008, 2952, 2918, 2849, 2227, 1716, 1700, 1591, 1436, 1343, 1270, 1158, 1042, and 969 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{21}H_{21}NNaO_6S^+$ $[M+Na^+]$ 438.0987, found 438.0990.

TLC: R_f 0.1 (2:1 hexanes:EtOAc).

mp: 162-170 °C.

Data for 217p

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, *J* = 2.0 Hz, 1H, Ar*H2*), 7.42 (d, *J* = 2.0 Hz, 1H, Ar*H6*), 7.18 (s, 1H, Ar*H7′*), 5.62 (br s, 2H, O*H*), 4.08–3.96 (m, 2H, NCH_2), 3.87 (s, 3H,

OC*H*$_3$), 3.27–3.20 (m, 2H, NCH$_2$C*H*$_2$), 2.89 (s, 3H, O$_2$SC*H*$_3$), 2.17 (s, 3H, ArC*H*$_3$), and 2.14 (s, 3H, ≡CC*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 166.8, 144.7, 143.5, 139.9, 134.8, 134.5, 134.1, 127.7, 124.2, 122.7, 122.6, 116.0, 114.1, 95.0, 75.8, 52.1, 50.3, 34.8, 28.4, 17.5, and 4.6.

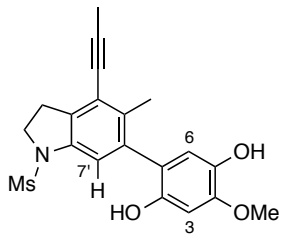
IR (neat): 3399, 2957, 2922, 2855, 2232, 1718, 1697, 1595, 1438, 1342, 1290, 1155, 1112, 1063, 1005, and 973 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{21}H_{21}NNaO_6S^+$ [M+Na$^+$] 438.0987, found 438.0998.

TLC: R_f 0.05 (2:1 hexanes:EtOAc).

mp: amorphous

2-Methoxy-5-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)benzene-1,4-diol (217q)



A solution of sulfonamide **215** (40.0 mg, 0.162 mmol) and 2-methoxybenzene-1,4-diol (34.0 mg, 0.242 mmol) in 1,2-dichloroethane (8 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (2:1 hexanes:EtOAc) to give benzenediol **217q** (47.2 mg, 75.3%) as a light yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (s, 1H, Ar*H7′*), 6.63 (s, 1H, Ar*H3*(or *H6*)), 6.54 (s, 1H, Ar*H6*(or *H3*)), 5.21 (s, 1H, O*H*), 4.35 (s, 1H, O*H*), 4.08–3.94 (m, 2H, NCH_2), 3.90 (s, 3H, OCH_3), 3.25–3.19 (m, 2H, NCH_2CH_2), 2.87 (s, 3H, O_2SCH_3), 2.19 (s, 3H, ArCH_3), and 2.14 (s, 3H, ≡CCH_3).

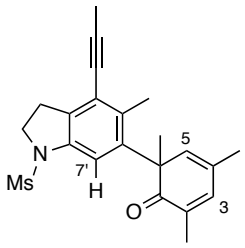
^{13}C NMR (125 MHz, $CDCl_3$): δ 147.0, 145.8, 140.0, 139.2, 135.6, 134.5, 134.2, 122.6, 119.1, 115.2, 114.8, 99.2, 94.9, 75.9, 56.0, 50.3, 34.6, 28.3, 17.5, and 4.6.

IR (neat): 3452, 3012, 2960, 2925, 2852, 2227, 1595, 1508, 1458, 1345, 1267, 1202, 1156, 1028, and 971 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{20}H_{21}NNaO_5S^+$ [M+Na^+] 410.1038, found 410.1036.

TLC: R_f 0.1 (2:1 hexanes:EtOAc).

2,4,6-Trimethyl-6-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)cyclohexa-2,4-dien-1-one (224)



A solution of sulfonamide **215** (100 mg, 0.404 mmol) and 2,4,6-trimethylphenol (275 mg, 2.02 mmol) in 1,2-dichloroethane (20 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by flash chromatography (2:1 hexanes:EtOAc) to give dienone **224** (135 mg, 87.3%) as a light yellow foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (s, 1H, Ar*H7′*), 6.80 (dq, *J* = 2.3, 1.3 Hz, 1H, *H3*), 5.83 (br s, 1H, *H5*), 4.05 (ddd, *J* = 10.6, 8.7, 7.3 Hz, 1H, NCH_aH$_b$), 3.91 (ddd, *J* = 10.5, 9.4, 8.5 1H, NCH$_a$$H_b$), 3.19-3.11 (m, 2H, NCH_2CH_2), 2.87 (s, 3H, O_2SCH_3), 2.07 (br s, 3H, ≡CCH_3), 1.97 (s, 3H, C2-CH_3), 1.93 (d, *J* = 1.5 Hz, 3H, C4-CH_3), 1.87 (s, 3H, ArCH_3), and 1.51 (s, 3H, C6-CH_3).

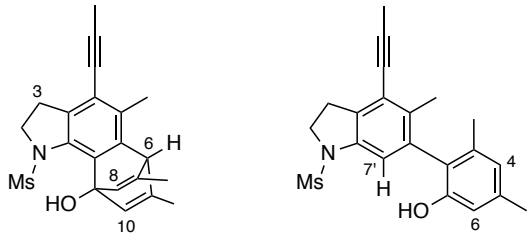
^{13}C NMR (125 MHz, $CDCl_3$): δ 203.7, 141.7, 141.5, 140.1, 139.7, 134.5, 132.79, 132.77, 127.3, 122.5, 111.6, 94.0, 76.4, 55.3, 50.5, 34.4, 28.2, 25.3, 20.9, 16.9, 15.7, and 4.5.

IR (neat): 3022, 2976, 2919, 2868, 2225 (w), 1662, 1648, 1592, 1452, 1345, 1159, and 969 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{22}H_{26}NO_3S^+$ [M+H$^+$] requires 384.1628; found 384.1685.

TLC: R_f 0.1 (2:1 hexanes:EtOAc).

5,7,11-Trimethyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)-1,2,3,6-tetrahydro-9*H*-6,9-ethenobenzo[*g*]indol-9-ol ($223_{[4+2]}$) and 3,5-Dimethyl-2-(5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)phenol (223_{ene})



A solution of sulfonamide **215** (25.0 mg, 0.101 mmol) and 3,5-dimethylphenol (37.0 mg, 0.303 mmol) in 1,2-dichloroethane (5 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (3:1 hexanes:EtOAc) to provide a coeluting mixture (ca. 2:1, ^{1}H NMR and GC-MS analyses) of compounds $\mathbf{223_{[4+2]}}$ and $\mathbf{223_{ene}}$ (30.4 mg, 81.5%). A portion of this mixture was separated by reverse phase MPLC (65:35 MeOH:H_2O) to give, in order of elution, indolol $\mathbf{223_{[4+2]}}$ (10.4 mg, 27.9%) and the biarylphenol $\mathbf{223_{ene}}$ (20.0 mg, 53.6%), each as an amorphous white solid.

Data for $223_{[4+2]}$

^{1}H NMR (500 MHz, $CDCl_3$, containing a small amount (<10% of $\mathbf{223_{ene}}$) δ 6.27 (dq, *J* = 1.6, 1.6 Hz, 2H, *H8* and *H10*), 5.69 (s, 1H, O*H*), 4.42 (t, *J* = 2.0 Hz, 1H, *H6*), 4.09 (t, *J* = 7.3 Hz, 2H, NCH_2), 2.99 (t, *J* = 7.4 Hz, 2H, NCH_2CH_2), 2.69 (s, 3H, O_2SCH_3), 2.48 (s, 3H, ArCH_3), 2.10 (s, 3H, ≡CCH_3), and 1.89 (d, *J* = 1.6, 6H, C7-CH_3 and C11-CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 146.5, 145.9, 142.7, 136.9, 135.8, 131.2, 130.4, 116.6, 92.6, 83.9, 76.5, 56.3, 52.4, 35.8, 29.2, 19.5, 16.6, and 4.6.

Difference nOe experiments showed a strong enhancement of the ArMe (as well as allylic methyl group) protons by H6 as well as of H8, H10, and the mesyl protons by the OH proton. This establishes the constitution of $\mathbf{223_{[4+2]}}$ to be as shown.

IR (neat): 3469, 2968, 2922, 2849, 2244, 1668, 1589, 1444, 1377, 1327, 1290, 1226, 1150, 1118, 1057, 1013, 972, and 914 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{21}H_{23}NNaO_3S^+$ [M+Na$^+$] 392.1296, found 392.1300.

TLC: R_f 0.2 (3:1 hexanes:EtOAc).

Data for 223_{ene}

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.12 (s, 1H, Ar*H7′*), 6.67 (br s, 1H, Ar*H4*(or *H6*)), 6.64 (br s, 1H, Ar*H6*(or *H4*)), 4.40 (br s, 1H, O*H*), 4.02^{+} (ddd, *J* = 10.5, 8.3, 8.3 Hz, 1H, NC*H*$_a$H$_b$), 4.02^{-} (ddd, *J* = 10.5, 8.0, 8.0 Hz, 1H, NCH$_a$*H*$_b$), 3.23^{+} (ddd, *J* = 16.7, 8.4, 8.4 Hz, 1H, NCH_2C*H*$_a$ H$_b$), 3.23^{-} (ddd, *J* = 16.7, 8.3, 8.3 Hz, 1H, NCH_2C*H*$_a$ H$_b$), 2.85 (s, 3H, O_2SC*H*$_3$), 2.31 (s, 3H, C5-C*H*$_3$), 2.14 (s, 3H, C5'-C*H*$_3$), 2.09 (s, 3H, ≡CC*H*$_3$) and 1.93 (s, 3H, C3-C*H*$_3$).

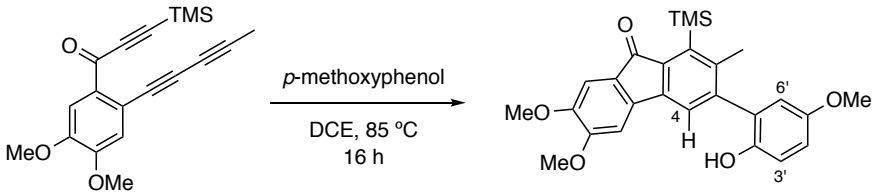
^{13}C NMR (125 MHz, $CDCl_3$): δ 152.3, 140.3, 138.7, 136.7, 134.9, 134.5, 134.2, 124.2, 123.0, 122.7, 114.8, 113.2, 94.9, 75.9, 50.4, 34.5, 28.3, 21.2, 19.9, 17.0, and 4.6.

IR (neat): 2963, 2919, 2855, 2229, 1621, 1586, 1455, 1417, 1345, 1229, 1155, 1106, 1049, 1004, 981, and 969 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{21}H_{23}NNaO_3S^{+}$ [M+Na^{+}] 392.1296, found 392.1302.

TLC: R_f 0.2 (3:1 hexanes:EtOAc).

3-(2-Hydroxy-5-methoxyphenyl)-6,7-dimethoxy-2-methyl-1-(trimethylsilyl)-9*H*-fluoren-9-one (227)



A solution of ynone **226** (30.0 mg, 0.0924 mmol) and *p*-methoxyphenol (34.4 mg, 2.02 mmol) in 1,2-dichloroethane (5 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (3:1 hexanes:EtOAc) to give fluorenone **227** (31.3 mg, 75.6%) as an orange amorphous foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (s, 1H, Ar*H4*), 7.16 (s, 1H, Ar*H8*), 6.93 (d, *J* = 8.9 Hz, 1H, Ar*H3′*), 6.91 (s, 1H, Ar*H5*), 6.87 (dd, *J* = 8.9, 3.1 Hz, 1H, Ar*H4′*), 6.69 (d, *J* = 3.1 Hz, 1H, Ar*H6′*), 4.48 (br s, 1H, O*H*), 3.96 (s, 3H, C6OC*H*$_3$; nOe H5), 3.92 (s, 3H, C7OC*H*$_3$; nOe H8), 3.80 (s, 3H, C5′OC*H*$_3$), 2.25 (s, 3H, ArC*H*$_3$), and 0.45 (s, 9H, Si(C*H*$_3$)$_3$).

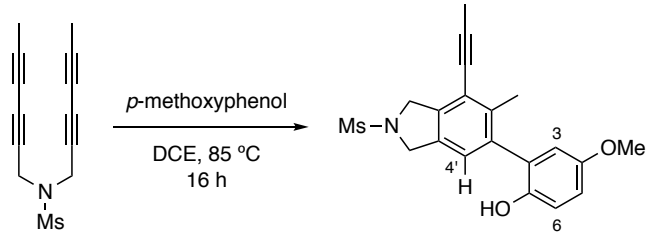
^{13}C NMR (125 MHz, $CDCl_3$): δ 194.3, 154.6, 153.6, 149.7, 146.2, 143.0, 142.9, 142.3, 141.0, 140.8, 138.6, 129.1, 126.6, 122.1, 116.4, 114.9, 114.7, 106.9, 102.7, 56.3, 56.2, 55.8, 21.8, and 2.8.

IR (neat): 3446, 2998, 2946, 2905, 2836, 1702, 1686, 1591, 1494, 1465, 1421, 1372, 1315, 1287, 1244, 1215, 1170, 1106, 877, and 847 cm^{-1}.

HRMS (ESI-TOF): Calcd for $C_{26}H_{28}NaO_5Si^+$ [M+Na$^+$] requires 471.1604; found 471.1610.

TLC: R_f 0.1 (3:1 hexanes:EtOAc).

4-Methoxy-2-(6-methyl-2-(methylsulfonyl)-7-(prop-1-yn-1-yl)isoindolin-5-yl)phenol (228)



A solution of sulfonamide **144** (40.0 mg, 0.162 mmol) and *p*-methoxyphenol (60.2 mg, 0.485 mmol) in 1,2-dichloroethane (8 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (2:1 hexanes:EtOAc) to give phenol **228** (32.6 mg, 54.3%) as an amorphous white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05 (s, 1H, Ar*H4'*), 6.89 (d, *J* = 8.7 Hz, 1H, Ar*H6*), 6.85 (dd, *J* = 9.0, 2.9 Hz, 1H, Ar*H5*), 6.61 (d, *J* = 2.9 Hz, 1H, Ar*H3*), 4.79-4.76 (m, 2H, C1'-H_2), 4.73 (br s, 2H, C3'-H_2), 4.33 (br s, 1H, O*H*), 3.77 (s, 3H, OCH_3), 2.91 (s, 3H, O_2SCH_3), 2.25 (s, 3H, ArCH_3), and 2.14 (s, 3H, ≡CCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 153.5, 146.4, 139.2, 138.8, 136.5, 133.7, 127.9, 127.2, 123.4, 116.2, 115.2, 114.8, 95.6, 77.2, 55.8, 54.3, 54.2, 34.9, 17.8, and 4.6.

A difference nOe experiment showed enhancement of the C3'-methylene and C3-arene protons upon irradiation of H4', allowing assignment of the constitution shown for **228**.

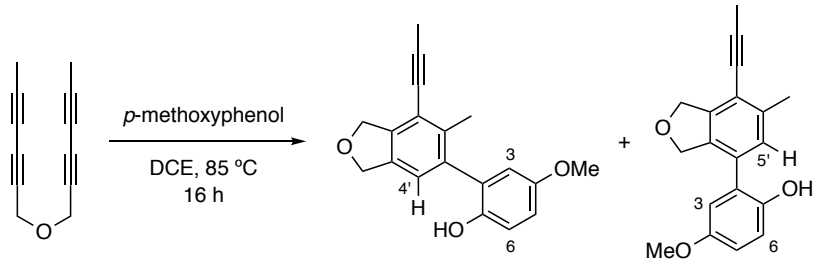
IR (neat): 3425, 2949, 2925, 2846, 2235, 1589, 1506, 1463, 1416, 1332, 1270, 1206, 1150, 1081, 1038, 963, and 870 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{20}H_{21}NNaO_4S^+$ [M+Na^+] 394.1089, found 394.1108.

TLC: R_f 0.1 (2:1 hexanes:EtOAc).

4-Methoxy-2-(6-methyl-7-(prop-1-yn-1-yl)-1,3-dihydroisobenzofuran-5-yl)phenol (229) and

4-Methoxy-2-(6-methyl-7-(prop-1-yn-1-yl)-1,3-dihydroisobenzofuran-4-yl)phenol (229′)



A solution of ynone **139a** (28.0 mg, 0.165 mmol) and *p*-methoxyphenol (78.8 mg, 0.635 mmol) in 1,2-dichloroethane (10 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (4:1 hexanes:EtOAc) to give a coeluting mixture of an ca. 6:1 ratio of phenols **229** to **229′** (19.2 mg, 40.5%) as a colorless solid.

Data for 229

^{1}H NMR (500 MHz, $CDCl_3$, major isomer): δ 7.02 (s, 1H, Ar*H4′*), 6.90 (d, *J* = 8.8 Hz, 1H, Ar*H6*), 6.84 (dd, *J* = 8.9, 3.0 Hz, 1H, Ar*H5*), 6.63 (d, *J* = 3.1 Hz, 1H, Ar*H3*), 5.18-5.06 (overlapping m, 4H, CH_2OCH_2), 4.62 (br s, 1H, O*H*), 3.77 (s, 3H, OCH_3), 2.25 (s, 3H, $ArCH_3$), and 2.13 (s, 3H, $\equiv CCH_3$). Difference nOe interaction observed from H4' to ArH3, OH, and $C(H3')_2$.

^{13}C NMR (125 MHz, $CDCl_3$): δ 153.3, 146.6, 142.1, 138.1, 136.8, 135.6, 128.3, 121.8, 118.6, 116.1, 115.2, 114.7, 94.4, 75.8, 74.1 (2x), 55.8, 17.6, and 4.6.

IR (neat, mixture): 3355, 2948, 2919, 2858, 2229, 1618, 1589, 1496, 1461, 1420, 1368, 1345, 1271, 1206, 1148, 1114, 1087, 1041, 1002, 985, and 896 cm^{-1}.

HRMS (ESI-TOF, mixture): Calcd for $C_{19}H_{18}NaO_3^+$ [$M+Na^+$] requires 317.1154; found 317.1161.

TLC: R_f 0.2 (3:1 hexanes:EtOAc).

Data for 229′

^{1}H NMR (500 MHz, $CDCl_3$, minor isomer): δ 7.09 (s, 1H, Ar*H5′*), 6.88 (d, *J* = 8.8 Hz, 1H, Ar*H6*), 6.81 (dd, *J* = 8.8, 3.1 Hz, 1H, Ar*H5*), 6.67 (d, *J* = 3.0 Hz, 1H, Ar*H3*), 5.18-5.06 (overlapping m, 4H, CH_2OCH_2), 4.85 (br s, 1H, O*H*), 3.76 (s, 3H, OCH_3), 2.45 (s,

3H, ArC*H*$_3$), and 2.13 (s, 3H, ≡CC*H*$_3$). Difference nOe interaction observed from H5' to ArH3 and ArCH$_3$.

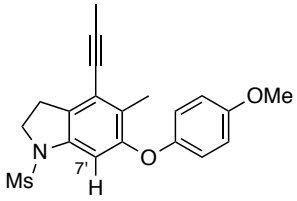
^{13}C NMR (125 MHz, $CDCl_3$): δ 153.5, 146.3, 142.8, 139.9, 135.8, 129.6, 129.5, 126.5, 117.3, 116.7, 115.0, 114.6, 94.3, 75.6, 74.3, 74.0, 55.8, 20.0, and 4.7.

IR (neat, mixture): 3355, 2948, 2919, 2858, 2229, 1618, 1589, 1496, 1461, 1420, 1368, 1345, 1271, 1206, 1148, 1114, 1087, 1041, 1002, 985, and 896 cm^{-1}.

HRMS (ESI-TOF, mixture): Calcd for $C_{19}H_{18}NaO_3^+$ [M+Na$^+$] requires 317.1154; found 317.1161.

TLC: R_f 0.2 (3:1 hexanes:EtOAc).

6-(4-Methoxyphenoxy)-5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indoline (225)



A solution of sulfonamide **215** (25.0 mg, 0.101 mmol), *p*-methoxyphenol (37.6 mg, 0.303 mmol) and Cs_2CO_3 (49.4 mg, 0.152 mmol) in benzene (5 mL) was heated in an 85 °C bath in a screw-capped culture tube equipped with a stir bar. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (3:1 hexanes:EtOAc) to give indoline **225** (24.7 mg, 65.8%) as an amorphous white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.91 (s, 1H, Ar*H7′*), 6.84–6.79 (m, 4H, Ar*H*), 3.97 (t, *J* = 8.5 Hz, 2H, NCH_2), 3.77 (s, 3H, OCH_3), 3.23 (t, *J* = 8.5 Hz, 2H, NCH_2CH_2), 2.78 (s, 3H, O_2SCH_3), 2.27 (s, 3H, ArCH_3), and 2.13 (s, 3H, ≡CCH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.2, 154.8, 151.3, 140.2, 129.0, 126.9, 122.5, 118.2, 114.9, 105.5, 94.5, 75.7, 55.7, 50.6, 34.2, 27.9, 13.7, and 4.6.

IR (neat): 3009, 2957, 2925, 2843, 2224, 1595, 1505, 1458, 1342, 1327, 1249, 1205, 1159, 1124, 1092, 1034, and 976 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{20}H_{21}NNaO_4S^+$ [M+Na^+] 394.1089, found 394.1091.

TLC: R_f 0.2 (3:1 hexanes:EtOAc).

Discussion of Computational Results

DFT computations were performed with the Gaussian 09 software package.[132] The geometries were optimized with the M06-2X functional;[133] the basis set was double-ζ split-valence 6-311+G(d, p). The SMD continuum solvation model[134] with 1,2-dichloroethane as solvent was applied during both the frequency calculation and the geometry optimization. Harmonic vibrational frequency calculations were performed at 298 K and used for the thermal correction of enthalpies. The value for the "Sum of electronic and thermal Free Energies=" was used to as the free energy (G) of the transition state structures (G_{TS}) as well as of the reactants and products. The optimized transition state structure geometry contained only one imaginary frequency.

[132] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox. *Gaussian 09*, revision D.01; Gaussian, Inc.: Wallingford, CT, 2009.

[133] Zhao, Y.; Truhlar, D. G. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Acc.* **2008**, *120*, 215–241.

[134] Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B*, **2009**, *113*, 6378–6396.

Energies and Geometries of the species in Figures 1 and 2 (one per page).

o-benzyne (**101**)

phenol

dienone **219**

biaryl **208c**

[4+2] adduct **218**

TS$_{phenol\text{-}ene}$

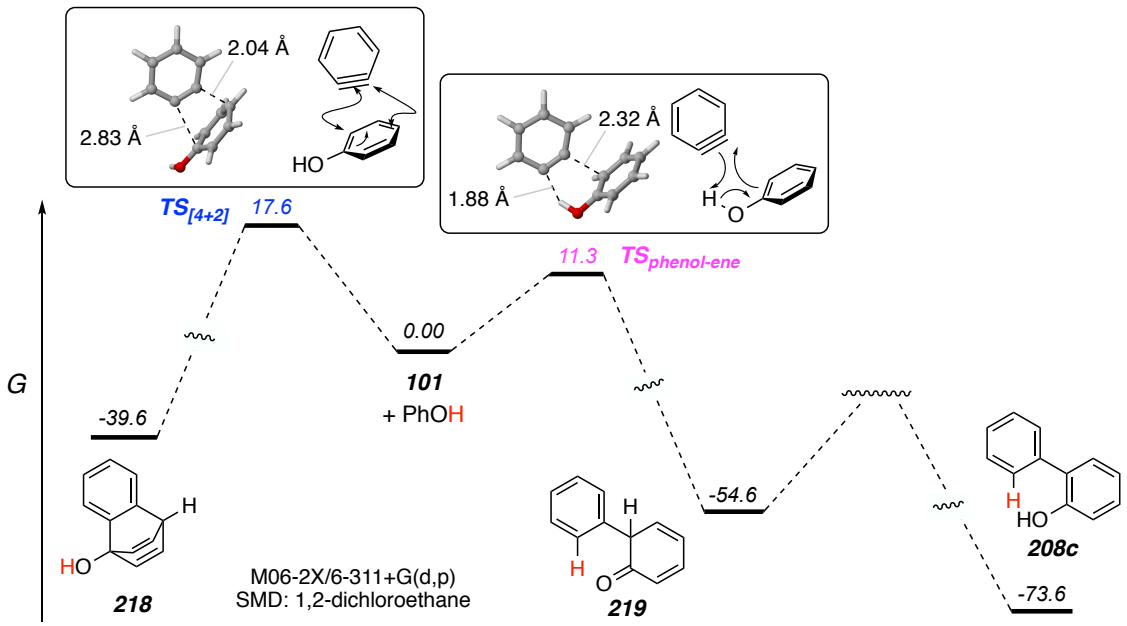
TS$_{[4+2]}$

220$_{para\text{-}bonding}$ (gas phase)

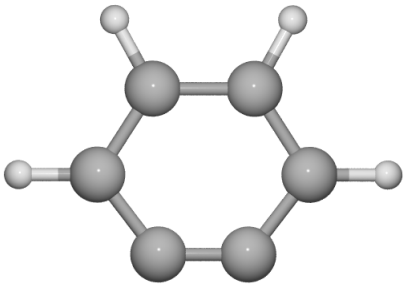
220$_{meta\text{-}bonding}$ (gas phase)

220$_{para\text{-}bonding}$ (DCE)

220$_{meta\text{-}bonding}$ (DCE)



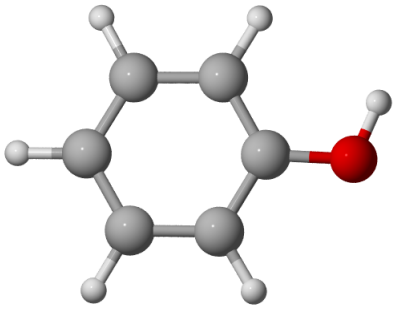
Geometry and free energy for benzyne (101)



Sum of electronic and thermal Free Energies = -230.821765 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.168096	0.014939	-0.014288
2	6	0	1.071753	0.016604	0.007682
3	6	0	1.912041	1.116005	0.024408
4	6	0	1.151276	2.298477	0.012901
5	6	0	-0.253880	2.296590	-0.011999
6	6	0	-1.011398	1.112080	-0.027396
7	1	0	2.993012	1.116270	0.043559
8	1	0	1.673825	3.248733	0.023739
9	1	0	-0.779034	3.245439	-0.019726
10	1	0	-2.092366	1.109441	-0.046555

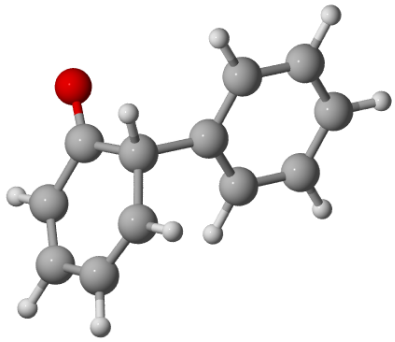
Geometry and free energy for phenol



Sum of electronic and thermal Free Energies = -307.353106 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.159181	-1.205425	-0.000581
2	6	0	-1.854020	-0.000413	0.022228
3	6	0	-1.142464	1.197768	0.007971
4	6	0	0.246279	1.196393	-0.028752
5	6	0	0.932615	-0.016426	-0.051323
6	6	0	0.232219	-1.220478	-0.037291
7	1	0	-1.698910	-2.145083	0.010212
8	1	0	-2.936336	0.006350	0.050742
9	1	0	-1.671976	2.143188	0.025387
10	1	0	0.811930	2.120304	-0.040283
11	1	0	0.772575	-2.161311	-0.055014
12	8	0	2.294541	0.035892	-0.086883
13	1	0	2.659069	-0.854906	-0.100924

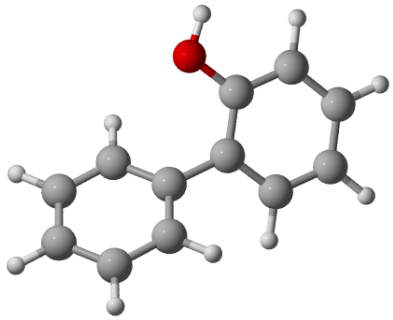
Geometry and free energy for dienone 219



Sum of electronic and thermal Free Energies = -538.261813 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.745527	0.081050	0.369148
2	6	0	1.005851	-0.964321	-0.519459
3	6	0	2.307264	-1.230989	-0.928983
4	6	0	3.362662	-0.458490	-0.449657
5	6	0	3.108160	0.583750	0.435763
6	6	0	1.803462	0.854567	0.841285
7	1	0	2.497602	-2.042477	-1.621581
8	1	0	4.377697	-0.669020	-0.764973
9	1	0	3.924556	1.187584	0.814267
10	1	0	1.607639	1.668585	1.530565
11	6	0	-2.927487	-0.774989	-0.604255
12	6	0	-2.448491	0.387647	-1.082406
13	6	0	-1.384851	1.106697	-0.372487
14	6	0	-0.689974	0.388114	0.787958
15	6	0	-1.377267	-0.858003	1.265151
16	6	0	-2.408058	-1.399661	0.609888
17	1	0	-3.736610	-1.275357	-1.126223
18	1	0	-2.850698	0.855489	-1.973101
19	1	0	-0.971015	-1.325712	2.155991
20	1	0	-2.872479	-2.313327	0.959818
21	8	0	-1.039832	2.229584	-0.688847
22	1	0	0.185455	-1.571901	-0.889303
23	1	0	-0.644798	1.110566	1.609459

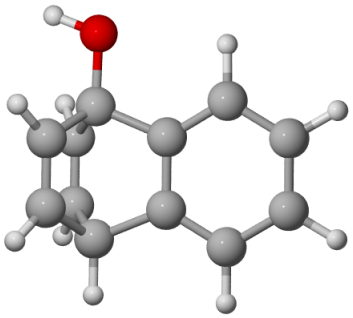
Geometry and free energy for biaryl 208c



Sum of electronic and thermal Free Energies = -538.292131 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.843526	-0.196774	-0.002659
2	6	0	1.554714	-1.315153	-0.449001
3	6	0	2.945555	-1.334734	-0.415746
4	6	0	3.647627	-0.234548	0.066942
5	6	0	2.948773	0.884312	0.514344
6	6	0	1.559274	0.905473	0.477283
7	1	0	3.479077	-2.208267	-0.772199
8	1	0	4.730750	-0.247565	0.093529
9	1	0	3.487900	1.743620	0.896363
10	1	0	1.022213	1.777727	0.828977
11	6	0	-3.450000	-0.316643	-0.019432
12	6	0	-2.790344	0.806772	-0.502629
13	6	0	-1.398031	0.861631	-0.497333
14	6	0	-0.642306	-0.215058	-0.007679
15	6	0	-1.331678	-1.333053	0.469820
16	6	0	-2.720432	-1.395206	0.469470
17	1	0	-4.533059	-0.344077	-0.027328
18	1	0	-3.353160	1.648064	-0.894569
19	1	0	-0.756588	-2.164089	0.863780
20	1	0	-3.226158	-2.272887	0.851896
21	1	0	1.013089	-2.170663	-0.838073
22	8	0	-0.730148	1.944180	-0.986449
23	1	0	-1.359584	2.588693	-1.326166

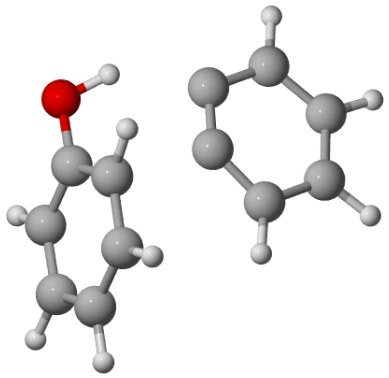
Geometry and free energy for [4+2] adduct 218



Sum of electronic and thermal Free Energies = -538.238038 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.776492	-0.660162	0.136832
2	6	0	-1.442166	0.229529	-0.711985
3	6	0	-1.311529	1.593097	-0.531261
4	6	0	-0.504175	2.066531	0.512433
5	6	0	0.154137	1.177978	1.351715
6	6	0	0.020819	-0.205300	1.167427
7	1	0	-1.826217	2.286708	-1.187363
8	1	0	-0.394871	3.134129	0.663029
9	1	0	0.775712	1.554867	2.155376
10	1	0	0.529535	-0.908412	1.815841
11	6	0	-2.575574	-2.252549	-0.188170
12	6	0	-1.048423	-2.118839	-0.225990
13	6	0	-2.267648	-0.491127	-1.780092
14	6	0	-3.208181	-1.411143	-0.995437
15	1	0	-3.032507	-2.973199	0.479199
16	1	0	-2.787128	0.196543	-2.442438
17	1	0	-4.281770	-1.332906	-1.102318
18	8	0	-0.362193	-2.976931	0.649705
19	1	0	-0.547219	-3.888054	0.400853
20	6	0	-1.267786	-1.398267	-2.504083
21	6	0	-0.633920	-2.239271	-1.697393
22	1	0	-1.107227	-1.311617	-3.570309
23	1	0	0.131947	-2.951263	-1.980269

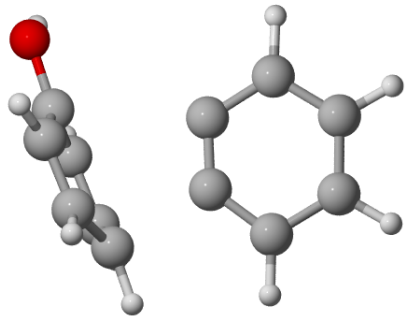
Geometry and free energy for $TS_{phenol\text{-}ene}$



Sum of electronic and thermal Free Energies = -538.156828 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.953518	-0.064829	0.315898
2	6	0	1.263599	-1.375649	0.055339
3	6	0	2.606567	-1.462347	-0.340643
4	6	0	3.423198	-0.324581	-0.423047
5	6	0	2.943668	0.952412	-0.116199
6	6	0	1.594087	1.035292	0.272635
7	1	0	3.014741	-2.437061	-0.583565
8	1	0	4.454932	-0.442922	-0.735724
9	1	0	3.593289	1.817422	-0.187446
10	6	0	-2.713403	-0.539368	-1.083079
11	6	0	-2.144177	0.717940	-1.024200
12	6	0	-1.401206	1.091641	0.104712
13	6	0	-1.198869	0.167937	1.146040
14	6	0	-1.804526	-1.100931	1.075203
15	6	0	-2.539668	-1.459565	-0.035548
16	1	0	-3.297881	-0.820449	-1.951456
17	1	0	-2.263221	1.434216	-1.827775
18	1	0	-1.677925	-1.794233	1.898403
19	1	0	-2.995256	-2.440112	-0.097761
20	8	0	-0.849832	2.315081	0.162309
21	1	0	0.604760	-2.229398	0.134055
22	1	0	-0.732429	0.499606	2.065209
23	1	0	0.121597	2.193276	0.380261

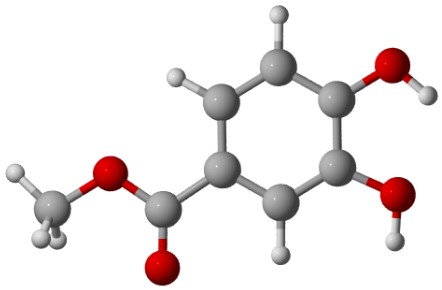
Geometry and free energy for $TS_{[4+2]}$



Sum of electronic and thermal Free Energies = -538.146787 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.530106	-0.469795	0.375695
2	6	0	-1.215493	0.263194	-0.437311
3	6	0	-1.321848	1.638458	-0.494117
4	6	0	-0.559808	2.286601	0.489104
5	6	0	0.205938	1.553442	1.400446
6	6	0	0.237319	0.150944	1.361204
7	1	0	-1.920235	2.191699	-1.209193
8	1	0	-0.567445	3.369775	0.539226
9	1	0	0.785530	2.081813	2.150827
10	1	0	0.842024	-0.392890	2.081139
11	6	0	-2.603687	-2.539857	-0.344959
12	6	0	-1.305858	-2.959991	-0.710233
13	6	0	-2.321712	-0.695574	-1.864697
14	6	0	-3.125605	-1.430187	-0.948915
15	1	0	-3.136585	-3.066711	0.438870
16	1	0	-2.761978	0.154992	-2.371409
17	1	0	-4.089718	-1.039399	-0.647266
18	8	0	-0.699322	-3.993256	-0.099407
19	1	0	-1.196422	-4.262256	0.681511
20	6	0	-1.227295	-1.365134	-2.484699
21	6	0	-0.697979	-2.473235	-1.887958
22	1	0	-0.751078	-0.922704	-3.351165
23	1	0	0.198489	-2.959586	-2.251389

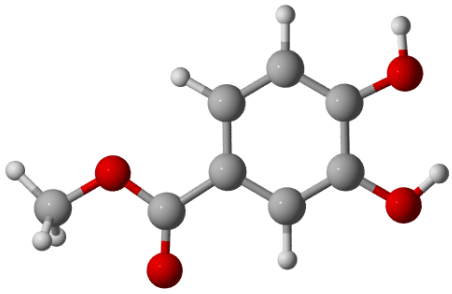
Geometry and free energy for methyl 3,4-dihydroxybenzoate ($220_{\text{para-bonding}}$) (gas phase)



Sum of electronic and thermal Free Energies = -610.399078 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.478338	-0.010777	-0.000110
2	6	0	-0.064807	-1.339871	-0.000076
3	6	0	1.290635	-1.645878	-0.000032
4	6	0	2.233213	-0.627873	-0.000005
5	6	0	1.811514	0.709548	0.000020
6	6	0	0.467620	1.017998	-0.000003
7	1	0	-0.803011	-2.130436	-0.000127
8	1	0	1.640635	-2.670481	-0.000060
9	1	0	0.125728	2.048171	0.000058
10	8	0	2.824264	1.631571	0.000161
11	1	0	2.467981	2.523592	-0.001630
12	8	0	3.550488	-0.925462	0.000014
13	1	0	4.052728	-0.101640	-0.000478
14	6	0	-1.910976	0.379456	-0.000189
15	8	0	-2.734640	-0.679190	-0.000091
16	8	0	-2.307169	1.517506	-0.000098
17	6	0	-4.127975	-0.368053	-0.000039
18	1	0	-4.387077	0.209536	-0.887744
19	1	0	-4.643408	-1.324834	-0.000102
20	1	0	-4.387039	0.209395	0.887770

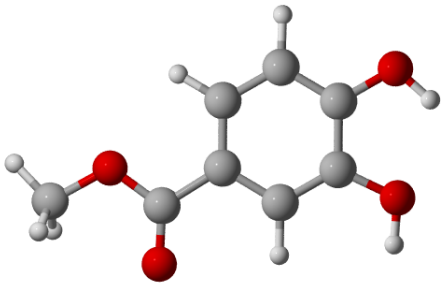
Geometry and free energy for methyl 3,4-dihydroxybenzoate ($220_{\text{meta-bonding}}$) (gas phase)



Sum of electronic and thermal Free Energies = -610.397549 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.479250	0.006449	-0.000079
2	6	0	-0.065767	-1.322568	-0.000107
3	6	0	1.292977	-1.617714	-0.000060
4	6	0	2.222205	-0.589187	0.000014
5	6	0	1.808615	0.749457	0.000042
6	6	0	0.457435	1.041374	-0.000004
7	1	0	-0.798823	-2.117266	-0.000165
8	1	0	1.633353	-2.648165	-0.000077
9	1	0	0.128964	2.073515	0.000016
10	8	0	2.722642	1.749492	0.000112
11	1	0	3.605181	1.361633	0.000114
12	8	0	3.575741	-0.771974	0.000070
13	1	0	3.793872	-1.707548	-0.000071
14	6	0	-1.919029	0.381120	-0.000128
15	8	0	-2.728841	-0.690550	-0.000094
16	8	0	-2.330792	1.511678	-0.000031
17	6	0	-4.125862	-0.397347	-0.000053
18	1	0	-4.392374	0.176956	-0.887714
19	1	0	-4.629511	-1.360501	-0.000125
20	1	0	-4.392350	0.176808	0.887713

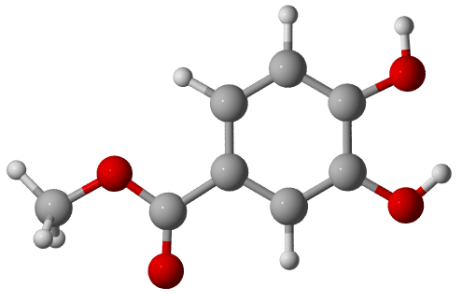
Geometry and free energy for methyl 3,4-dihydroxybenzoate ($220_{\text{para-bonding}}$) (DCE)



Sum of electronic and thermal Free Energies = -610.410634 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.271698	-1.081035	0.067756
2	6	0	-1.917409	0.096400	0.437683
3	6	0	-1.188047	1.269654	0.590239
4	6	0	0.182568	1.268097	0.374160
5	6	0	0.831405	0.080552	0.001362
6	6	0	0.109790	-1.086314	-0.150971
7	1	0	-2.985790	0.096886	0.605997
8	1	0	-1.667462	2.197427	0.877179
9	1	0	0.603938	-2.007995	-0.438845
10	8	0	2.177917	0.197403	-0.184084
11	1	0	2.568430	-0.645829	-0.435394
12	8	0	0.890589	2.410174	0.523060
13	1	0	1.821054	2.228629	0.335951
14	6	0	-2.003570	-2.360804	-0.108627
15	8	0	-3.313896	-2.243299	0.124657
16	8	0	-1.483823	-3.404614	-0.428457
17	6	0	-4.087033	-3.438879	-0.025980
18	1	0	-3.738331	-4.202870	0.668494
19	1	0	-5.111175	-3.156286	0.200221
20	1	0	-4.009259	-3.811494	-1.047099

Geometry for methyl 3,4-dihydroxybenzoate ($220_{\text{meta-bonding}}$) (DCE)



Sum of electronic and thermal Free Energies = -610.409599 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.212524	-1.203884	0.073185
2	6	0	-1.838315	0.032101	0.215652
3	6	0	-1.072430	1.191587	0.271954
4	6	0	0.309763	1.110634	0.185921
5	6	0	0.942170	-0.133564	0.042340
6	6	0	0.179963	-1.284515	-0.013432
7	1	0	-2.915944	0.091419	0.282422
8	1	0	-1.545792	2.160948	0.382701
9	1	0	0.667252	-2.245598	-0.124268
10	8	0	2.295081	-0.207547	-0.041318
11	1	0	2.660618	0.684342	0.014779
12	8	0	1.150921	2.177355	0.229877
13	1	0	0.665020	3.002842	0.329093
14	6	0	-1.985913	-2.471473	0.007980
15	8	0	-3.304925	-2.276669	0.100414
16	8	0	-1.490640	-3.566857	-0.115042
17	6	0	-4.117496	-3.454166	0.045378
18	1	0	-3.866682	-4.123578	0.867909
19	1	0	-5.143023	-3.107325	0.134622
20	1	0	-3.968906	-3.970248	-0.902864

Supplementary Information for Chapter 3

General Experimental Protocols

^{13}C and ^{1}H NMR spectra were taken on an HD-500 or AV-500 (500 MHz) spectrometer. ^{1}H chemical shifts solutions are referenced to TMS (δ 0.00 ppm) in $CDCl_3$ and to the residual CHD_5 (δ 7.15 ppm) in benzene-d_6. Where encountered, a non-first order multiplet in a ^{1}H NMR spectrum is denoted as 'nfom'. Resonances are reported in the following format: chemical shift (ppm) [multiplicity, coupling constant(s) (in Hz), integral (to the nearest integer), and assignment of the location within the structure]. This is indicated by, e.g., R^{1}C*Ha*Hb for diastereotopic geminal protons; arbitrarily, the more downfield resonance is labeled as H_a. Coupling constants have been analyzed using methods we have described elsewhere.[130,131] The ^{13}C NMR shifts are taken from the "1D" spectra.

Infrared spectra were recorded using a Midac Corporation (Prospect 4000) FT-IR spectrometer. Only the more diagnostic and/or intense peaks are reported; spectra were collected from samples as neat thin films deposited on a germanium window in the attenuated total reflectance (ATR) mode.

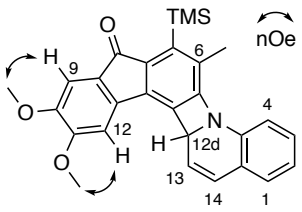
Some of the high-resolution **mass spectrometry** (HRMS) measurements were made on a Bruker BioTOF II (ESI-TOF) instrument in the electrospray ionization mode (ESI); poly(ethylene glycol) (PEG) or poly(propylene glycol) (PPG) was used as the standard/calibrant. Samples were infused as methanol solutions. HRMS data were collected as approximately ten separate data sets and then averaged to obtain the reported "found" value. The majority of the HRMS data were collected on a Thermo Orbitrap Velos instrument (having a mass accuracy of ≤3 ppm) in the ESI or atmospheric pressure chemical ionization (APCI) mode. An external calibrant (Pierce™ LTQ) was used; samples were introduced as a solution in acetonitrile or methanol.

Medium pressure liquid **chromatography** (MPLC) was performed on columns of silica gel (25-200 psi, 20-40 μm, 60 Å pore size, Teledyne RediSep Rf Gold® normal-phase silica) that had been hand packed. The device consisted of a Waters HPLC pump (M6000), a Gilson (112 UV) detector, and a Waters (R401) differential refractive index detector. Agela silica gel (230-400 mesh) was used to prepare flash chromatography columns. Silica gel thin layer chromatography (TLC) was performed on glass- or plastic-backed plates that were visualized UV illumination and/or by a solution of potassium permanganate or ceric ammonium molybdate (CAM) and heating.

Some compounds were purified by HPLC to achieve mg quantities of samples of high purity, from which the full characterization data set. A 1 cm diameter x 25 cm long column of silica gel (Alltech, Econosil, 10 μm) was used.

Reactions performed under anhydrous conditions were carried out in oven-dried glassware under an atmosphere of nitrogen. Anhydrous THF was dried by passage through a column of activated alumina before use. Reaction temperature refers to the temperature of the external heating or cooling bath unless otherwise noted. HDDA reactions, including ones performed at temperatures higher than the boiling point of the reaction solvent, were done in a screw-capped vial or culture tube that was capped with an inert, Teflon®-lined closure.

10,11-Dimethoxy-6-methyl-7-(trimethylsilyl)fluoreno[4',3':3,4]azeto[1,2-*a*]quinolin-8(12d*H*)-one (316)



A solution of ketone **226** (50.0 mg, 0.154 mmol) and quinoline (36.2 μL, 0.308 mmol) in benzene (10 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (3:1 hexanes:EtOAc) to give ketone **316** (27.2 mg, 38%) as an orange, foamy solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (br d, *J* = 7.9 Hz, 1H, Ar*H4*), 7.18 (ddd, *J* = 7.9, 6.9, 2.2 Hz, 1H, Ar*H3*), 7.16 (s, 1H, Ar*H9*), 7.01 (ddd, *J* = 7.5, 7.5, 1.2 Hz, 1H, Ar*H2*), 6.99 (br dd, *J* = 7.5, 2.2 Hz, 1H, Ar*H1*), 6.71 (s, 1H, Ar*H12*), 6.34 (dd, *J* = 10.0, 2.2 Hz, 1H, *H13* or *H14*, 6.17 (dd, *J* = 2.3, 2.3 Hz, 1H, *H12d*), 6.07 (dd, *J* = 10.0, 2.2 Hz, 1H, *H13* or *H14*), 4.00 (s, 3H, C11OC*H*$_3$), 3.92 (s, 3H, C10OC*H*$_3$), 2.36 (s, 3H, ArC*H*$_3$), and 0.39 [s, 9H, Si(C*H*$_3$)$_3$].

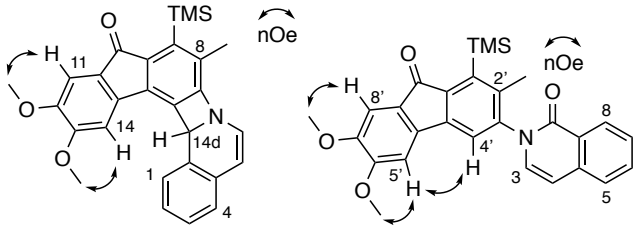
^{13}C NMR (125 MHz, $CDCl_3$): δ 192.7 (C8), 162.4 (C5a), 153.7, 149.8, 145.8, 139.4, 135.7, 134.4, 133.2, 132.7, 129.0 (C3), 128.8, 128.0 (C1), 127.1, 126.1 (C13 or C14), 124.8 (C2), 123.7, 123.4 (C13 or C14), 123.3 (C4), 106.9, 104.2, 68.9 (C12d), 56.4, 56.2, 17.8, and 2.8.

IR (neat): 2945, 2904, 2841, 1703, 1638, 1590, 1496, 1456, 1419, 1363, 1323, 1273, 1241, 1214, 1119, 1080, 1059, 1018, and 989 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{28}H_{28}NO_3Si^+$ [M+H$^+$] 454.1833, found 454.1830.

TLC: R_f 0.4 (2:1 hexanes:EtOAc).

12,13-Dimethoxy-8-methyl-9-(trimethylsilyl)fluoreno[4',3':3,4]azeto[2,1-*a*]isoquinolin-10(14d*H*)-one (313), and 2-(6,7-Dimethoxy-2-methyl-9-oxo-1-(trimethylsilyl)-9*H*-fluoren-3-yl)isoquinolin-1(2*H*)-one (314)



A solution of ketone **226** (50.0 mg, 0.154 mmol) and isoquinoline (36.2 μL , 0.308 mmol) in benzene (10 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (3:1 hexanes:EtOAc) to give the isoquinolinone **313** (3.6 mg, 5%) and isoquinolone **314** (15.5 mg, 22%), each as an orange, foamy solid.

Compound 313 (azetidene)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33–7.31 (nfom, 1H, Ar*H1*), 7.19 (s, 1H, Ar*H11*), 7.17–7.14 (m, 2H, Ar*H2* and Ar*H3*), 7.14 (s, 1H, Ar*H14*), 6.99–6.96 (nfom, 1H, Ar*H4*), 6.68 (s, 1H, *H14d*), 6.59 (d, *J* = 7.2 Hz, 1H, Ar*H6*), 5.73(d, *J* = 7.2 Hz, 1H, Ar*H5*), 4.06 (s, 3H, C13OCH_3), 3.93 (s, 3H, C12OCH_3), 2.27 (s, 3H, ArCH_3), and 0.40 [s, 9H, Si(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 192.7, 161.3, 153.4, 149.9, 145.1, 135.7, 135.5, 131.8, 131.6, 129.4, 128.6, 128.3, 127.6, 126.4, 126.0, 125.6, 125.1, 122.3, 110.5, 106.9, 104.6, 69.2, 56.4, 56.2, 17.5, and 2.7. (Some ^{13}C chemical shift values were obtained from the HSQC and HMBC data)

IR (neat): 2942, 2902, 2844, 1701, 1644, 1592, 1494, 1456, 1417, 1366, 1313, 1270, 1243, 1214, 1122, 1083, 1059, 1018, and 909 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{28}H_{28}NO_3Si^+$ [M+H$^+$] 454.1833, found 454.1832.

TLC: R_f 0.2 (3:1 hexanes:EtOAc).

Compound 314 (isoquinolone)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.49 (dddd, *J* = 8.1, 1.2, 0.5, 0.5 Hz, 1H, Ar*H8*), 7.72 (ddd, *J* = 8.0, 7.1, 1.4 Hz, 1H, Ar*H7*), 7.60 (br d, *J* = 8.0 Hz, 1H, Ar*H5*), 7.56 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, Ar*H6*), 7.29 (d, *J* = 0.5 Hz, 1H, *H4'*), 7.16 (s, 1H, Ar*H8'*), 7.02 (d, *J* = 7.4 Hz, 1H, Ar*H3*), 6.90 (s, 1H, Ar*H5'*), 6.63 (dd, *J* = 7.5, 0.5 Hz, 1H,

Ar*H4*), 3.94 (s, 3H, C6'OC*H₃*), 3.92 (s, 3H, C7'OC*H₃*), 2.20 (s, 3H, ArC*H₃*), and 0.45 [s, 9H, Si(C*H₃*)₃].

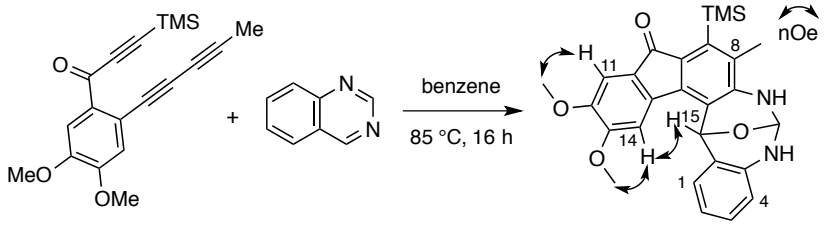
^{13}C NMR (125 MHz, $CDCl_3$): δ 193.8, 161.8, 154.6, 149.8, 144.1, 143.8, 143.4, 141.0, 140.8, 138.2, 137.2, 132.8, 131.6, 128.3, 127.4, 126.7, 126.5, 126.1, 119.7, 106.9, 106.7, 102.9, 56.3, 56.2, 19.2, and 2.8.

IR (neat): 3000, 2990, 2933, 2900, 2836, 1704, 1652, 1625, 1591, 1557, 1494, 1455, 1417, 1381, 1359, 1316, 1266, 1244, 1212, 1152, 1117, 1093, 1056, 1017, 1005, and 983 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{28}H_{28}NO_4Si^+$ [$M+H^+$] 470.1782, found 470.1773.

TLC: R_f 0.1 (3:1 hexanes:EtOAc).

12,13-Dimethoxy-8-methyl-9-(trimethylsilyl)-5,6,7,15-tetrahydro-10*H*-6,15-epoxybenzo[*d*]fluoreno[4,3-*g*][1,3]diazocin-10-one (322)



A solution of ketone **226** (30.0 mg, 0.0924 mmol) and quinazoline (24.0 mg, 0.185 mmol) in benzene (8 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (2:1 hexanes:EtOAc) to give ketone **322** (24.7 mg, 57%) as an orange, foamy solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (s, 1H, Ar*H14*), 7.32 (dd, *J* = 7.8, 1.0 Hz, 1H, Ar*H1*), 7.19 (s, 1H, Ar*H11*), 7.14 (ddd, *J* = 7.8, 7.8, 1.4 Hz, 1H, Ar*H3*), 6.82 (ddd, *J* = 7.6, 7.6, 1.1 Hz, 1H, Ar*H2*), 6.80 (dd, *J* = 7.8, 1.0 Hz, 1H, Ar*H4*), 6.67 (s, 1H, Ar*H15*), 6.18 (d, *J* = 2.7 Hz, 1H, *H6*), 5.06 (d, *J* = 2.7 Hz, 1H, N*H*), 4.84 (br s, 1H, N*H*), 4.03 (s, 3H, C13OC*H*$_3$), 3.94 (s, 3H, C12OC*H*$_3$), 2.16 (s, 3H, ArC*H*$_3$), and 0.38 [s, 9H, Si(C*H*$_3$)$_3$].

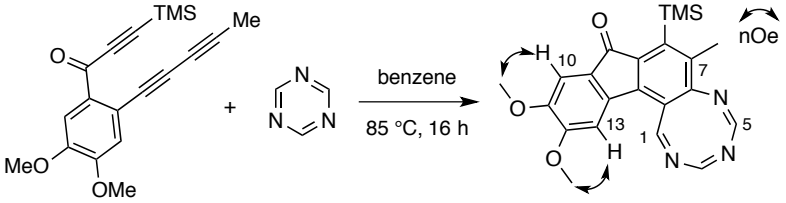
^{13}C NMR (125 MHz, $CDCl_3$): δ 192.3 156.0, 152.9, 149.3, 142.0, 137.6, 137.0, 130.3, 129.4, 128.4, 125.2, 124.3, 124.1, 121.0, 119.0, 118.2, 106.9, 106.0, 102.9, 82.1 (C6), 66.8 (C15), 56.5, 56.2, 17.4 (ArMe), and 2.9 (TMS). (indicated carbon assignments from HSQC and/or HMBC)

IR (neat): 3433, 3336, 2993, 2944, 2905, 2835, 1681, 1607, 1579, 1547, 1496, 1461, 1419, 1381, 1362, 1341, 1296, 1247, 1209, 1179, 1095, 1049, 1036, 1018, and 989 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{27}H_{29}N_2O_4Si^+$ [M+H$^+$] 473.1891, found 473.1882.

TLC: R_f 0.1 (2:1 hexanes:EtOAc).

(1*Z*,3*Z*,5*Z*)-11,12-Dimethoxy-7-methyl-8-(trimethylsilyl)-9*H*-fluoreno[3,4-*f*][1,3,5]triazocin-9-one (319)



A solution of ketone **226** (50.0 mg, 0.154 mmol) and 1,3,5-triazine (25.0 mg, 0.308 mmol) in benzene (10 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (2:1 hexanes:EtOAc) to give ketone **319** (20.8 mg, 33%) as an orange solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.62 (d, *J* = 0.8 Hz, 1H, Ar*H1*), 8.04 (s, 1H, Ar*H5*), 7.97 (d, *J* = 0.8 Hz, 1H, Ar*H3*), 7.18 (s, 1H, Ar*H10*), 6.80 (s, 1H, Ar*H13*), 3.99 (s, 3H, C12OCH_3), 3.93 (s, 3H, C11OCH_3), 2.29 (s, 3H, ArCH_3), and 0.42 [s, 9H, Si(CH_3)$_3$].

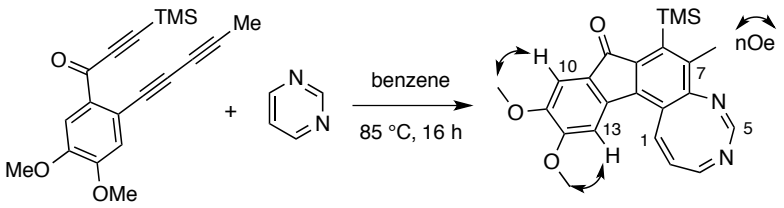
^{13}C NMR (125 MHz, $CDCl_3$): δ 193.1 (C9), 163.8 (C1), 159.7 (C3), 156.0 (C5), 154.0, 150.0, 148.7, 145.4, 139.9, 137.2, 137.1, 136.6, 127.5, 121.8, 107.1 (C10), 105.8 (C13), 56.5, 56.2, 19.8 (ArMe), and 2.6 (TMS). (indicated carbon assignments from HSQC and/or HMBC)

IR (neat): 2999, 2942, 2897, 2836, 1702, 1633, 1588, 1565, 1531, 1492, 1457, 1420, 1361, 1312, 1294, 1240, 1212, 1149, 1081, 1048, 1017, and 949 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{22}H_{24}N_3O_3Si^+$ [M+H$^+$] 406.1581, found 406.1579.

TLC: R_f 0.1 (2:1 hexanes:EtOAc).

(1*Z*,3*Z*,5*Z*)-11,12-Dimethoxy-7-methyl-8-(trimethylsilyl)-9*H*-fluoreno[3,4-*d*][1,3]diazocin-9-one (320)



A solution of ketone **226** (30.0 mg, 0.0924 mmol) and pyrimidine (14.8 μL, 0.185 mmol) in benzene (8 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (1:1 hexanes:EtOAc) to give ketone **320** (14.8 mg, 40%) as an orange solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (dd, *J* = 0.9, 0.9 Hz, 1H, Ar*H5*), 7.86 (dd, *J* = 1.1, 1.1 Hz, 1H, Ar*H3*), 7.16 (s, 1H, Ar*H10*), 6.99 (d, *J* = 11.7 Hz, 1H, Ar*H1*), 6.95 (s, 1H, Ar*H13*), 6.50 (ddd, *J* = 11.7, 1.2, 0.9 Hz, 1H, Ar*H2*), 3.98 (s, 3H, C12OCH_3), 3.91 (s, 3H, C11OCH_3), 2.33 (s, 3H, ArCH_3), and 0.42 [s, 9H, Si(CH_3)$_3$].

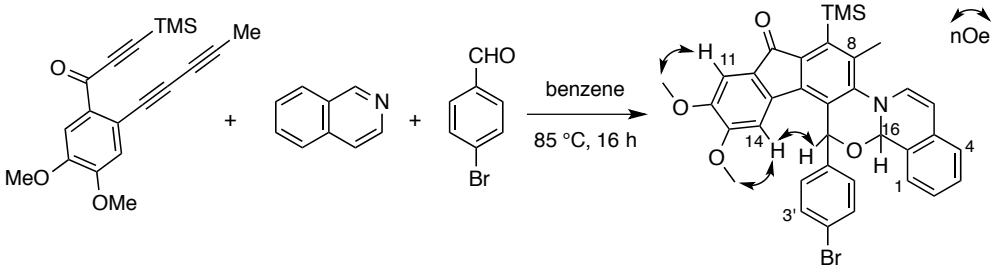
^{13}C NMR (125 MHz, $CDCl_3$): δ 193.8, 164.0, 157.3, 153.5, 149.7, 149.4, 142.5, 140.6, 138.1, 136.9, 136.2, 134.6, 130.7, 127.6, 123.0, 106.9, 106.7, 56.3, 56.2, 20.2, and 2.7.

IR (neat): 2998, 2941, 2899, 2835, 1702, 1637, 1590, 1560, 1525, 1492, 1465, 1416, 1367, 1312, 1246, 1213, 1182, 1149, 1081, 1039, 1019, and 968 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{23}H_{25}N_2O_3Si^+$ [M+H$^+$] 405.1629, found 405.1619.

TLC: R_f 0.1 (1:1 hexanes:EtOAc).

(±)-(15*R,16*R**)- and (±)-(15*R**,16*S**)-15-(4-Bromophenyl)-12,13-dimethoxy-8-methyl-9-(trimethylsilyl)-16a*H*-fluoreno[3',4':4,5][1,3]oxazino[2,3-*a*]isoquinolin-10(15*H*)-one (S5)**



A solution of ketone **226** (30.0 mg, 0.0924 mmol) isoquinoline (**301a**, 21.7 μL, 0.185 mmol), and *p*-bromobenzaldehyde (**S6**, 85.5 mg, 0.462 mmol) in benzene (5 mL) was heated in an 85 °C bath in a screw-capped culture tube. After 16 h the reaction mixture was concentrated and the residue was purified by MPLC (6:1 hexanes:EtOAc) to give the diastereomeric ketones **S5-maj** (23.9 mg, 41%) and **S5-min** (19.4 mg, 33%), each as an orange, foamy, amorphous solid.

S5-maj (faster eluting, major isomer)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (br s, 2H, Ar*H3'a* and Ar*H3'b*), 7.32 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H, Ar*H3*), 7.32 (br s, 1H, Ar*H2'a*), 7.19–7.10 (m, 3H, Ar*H2*, Ar*H4,* Ar*H2'b*), 7.12 (s, 1H, Ar*H11*), 6.73 (d, *J* = 7.6 Hz, 1H, Ar*H1*), 6.34 (dd, *J* = 7.7, 1.5 Hz, 1H, Ar*H6*), 6.17 (s, 1H, Ar*H14*), 6.14 (s, 1H, *H15*), 5.87 (d, *J* = 7.7 Hz, 1H, Ar*H5*), 5.74 (d, *J* = 1.4 Hz, 1H, *H16*), 3.86 (s, 3H, C12OC*H*$_3$), 3.45 (s, 3H, C13OC*H*$_3$), 2.48 (s, 3H, ArC*H*$_3$), and 0.49 [s, 9H, Si(C*H*$_3$)$_3$]. (rotation about the hindered *p*-BrC_6H_4–C bond was slow enough at ambient temperature to broaden the four ArH resonances on the *p*-BrC_6H_4 ring.)

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.6, 153.3, 149.0, 145.7, 143.4, 140.1, 139.7, 136.7, 136.3, 134.9, 133.1, 131.1, 130.7, 129.7, 128.3, 127.6, 126.1, 125.6, 125.1, 124.3, 122.92, 122.89, 108.3, 106.5, 102.1, 78.3, 75.2, 56.1, 56.0, 21.2, and 3.0.

IR (neat): 2999, 2932, 2903, 2848, 1702, 1633, 1591, 1569, 1535, 1493, 1457, 1431, 1400, 1367, 1314, 1284, 1244, 1211, 1120, 1098, 1057, 1031, 1009, and 958 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{35}H_{33}BrNO_4Si^+$ [M+H$^+$] 638.1357, found 638.1343.

TLC: R_f 0.2 (6:1 hexanes:EtOAc).

S5-min (slower eluting, minor isomer)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (superposition of two doublets: d, *J* = 8.5 Hz, 2H, H3' and d, *J* ca. 8 Hz, 1H, H4), 7.34 (ddd, *J* = 7.4, 7.4, 1.3 Hz, 1H, *H2* or *H3*), 7.24 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H, *H2* or *H3*), 7.15 (superposition of two doublets: d, *J* = 8.4 Hz, 2H, H2' and d, *J* ca. 8 Hz, 1H, H1), 7.12 (s, 1H, Ar*H11*), 6.64 (s, 1H, *H15*), 6.58 (s, 1H, Ar*H14*), 6.46 (dd, *J* = 7.5, 1.3 Hz, 1H, Ar*H6*), 6.06 (d, *J* = 1.1 Hz, 1H, *H16*), 5.86 (d, *J* = 7.6 Hz, 1H, Ar*H5*), 3.86 (s, 3H, C13OCH_3), 3.73 (s, 3H, C12OCH_3), 2.42 (s, 3H, ArCH_3), and 0.48 [s, 9H, Si(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.5, 153.4, 149.2, 146.2, 143.4, 140.0, 139.3, 137.7, 136.9, 136.1, 132.0, 131.7, 131.3, 129.6, 129.5, 128.3, 127.4, 126.6, 126.0, 125.7, 124.6, 122.6, 108.1, 106.7, 102.0, 83.0, 77.0, 56.3, 56.1, 20.2, and 2.6.

IR (neat): 3006, 2940, 2894, 1702, 1630, 1590, 1566, 1538, 1492, 1458, 1433, 1404, 1360, 1312, 1285, 1241, 1210, 1119, 1098, 1059, 1031, 1009, and 986 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{35}H_{33}{}^{79}BrNO_4Si^+$ [M+H$^+$] 638.1357, found 638.1336.

TLC: R_f 0.1 (6:1 hexanes:EtOAc).

Discussion of Computational Results

The Gaussian 09 software package was used to perform the DFT computations.[132] The geometries were optimized using the M06-2X functional;[133] the double-ζ split-valence 6-311+G(d, p) basis set was used. The SMD solvation model[134] with benzene as solvent was applied during the both frequency calculation as well as the geometry optimization. Harmonic vibrational frequency calculations were done at 298 K and were used for thermal correction of enthalpies. The "Sum of electronic and thermal Free Energies=" value was used as the free energy (G) of the transition state structures as well as that of the reactants and products. The optimized transition structure geometry showed only one imaginary frequency.

Energies and Geometries of the species.

3,6-dimethylbenzyne (**323**)

isoquinoline (**301a**)

zwitterion **324**

TS$_{protonshift}$

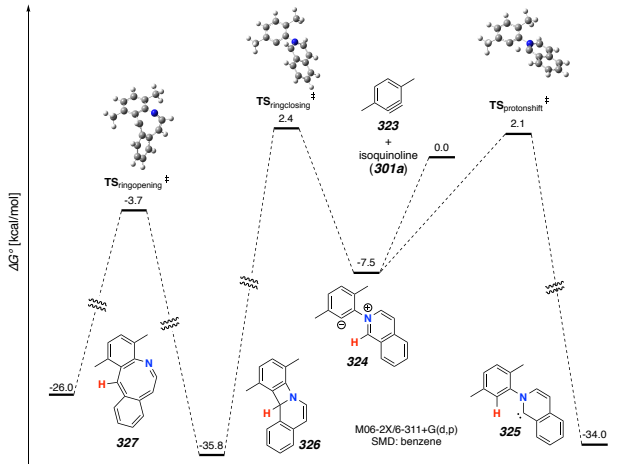
carbene **325**

TS$_{ringclosing}$

intermediate **326**

TS$_{ringopening}$

benzoazocine **327**



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quinoline (**301b**)

quinoline zwitterion **328**

TS$_{quinolinecarbene}$

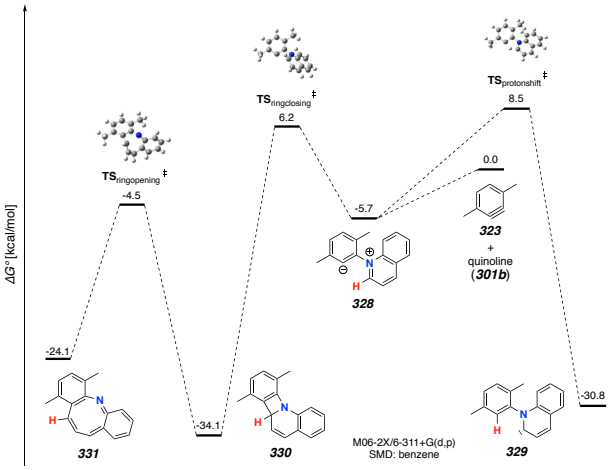
quinoline carbene **329**

TS$_{quinolineringclosing}$

quinoline azetidine **330**

TS$_{quinolineringopening}$

quinoline azocine **331**



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triazine (**301d**)

triazine zwitterion **332**

TS$_{triazinecarbene}$

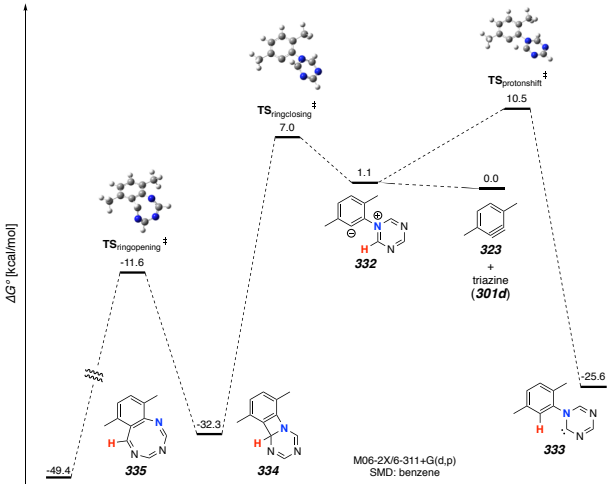
triazine carbene **333**

TS$_{triazineringclosing}$

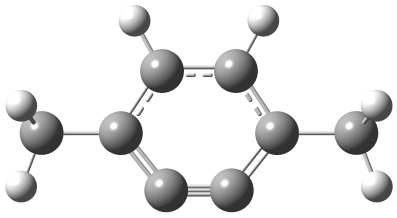
triazine azetidine **334**

TS$_{triazineringopening}$

triazine azocine **335**



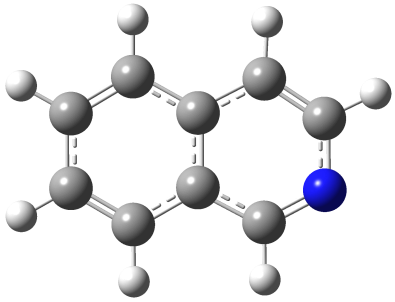
Geometry and free energy for 3,6-dimethylbenzyne (323)



Sum of electronic and thermal Free Energies = -309.384039 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.620715	-1.182510	0.000003
2	6	0	-0.620715	-1.182510	-0.000004
3	6	0	-1.480728	-0.097659	-0.000012
4	6	0	-0.700246	1.080424	-0.000004
5	6	0	0.700246	1.080424	0.000005
6	6	0	1.480728	-0.097659	0.000001
7	1	0	-1.220246	2.034668	-0.000012
8	1	0	1.220246	2.034668	0.000006
9	6	0	-2.981786	-0.094617	0.000004
10	1	0	-3.367096	0.421123	0.882560
11	1	0	-3.367110	0.422213	-0.881906
12	1	0	-3.369692	-1.111832	-0.000612
13	6	0	2.981786	-0.094617	0.000001
14	1	0	3.367103	0.421632	-0.882254
15	1	0	3.367103	0.421704	0.882212
16	1	0	3.369692	-1.111832	0.000042

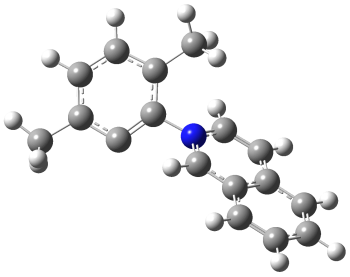
Geometry and free energy for isoquinoline (301a)



Sum of electronic and thermal Free Energies = -401.753046 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.405445	-0.707170	-0.000001
2	6	0	-1.222054	-1.396244	-0.000004
3	6	0	0.007660	-0.692327	-0.000002
4	6	0	0.010126	0.722934	0.000002
5	6	0	-1.229794	1.412534	0.000005
6	6	0	-2.406029	0.710303	0.000004
7	1	0	-3.348235	-1.240630	-0.000002
8	1	0	-1.208261	-2.480851	-0.000008
9	6	0	1.269999	1.371582	0.000004
10	1	0	-1.229396	2.496844	0.000009
11	1	0	-3.351763	1.239422	0.000006
12	6	0	2.411434	0.616995	0.000001
13	1	0	1.324344	2.453980	0.000007
14	1	0	3.387390	1.090132	0.000002
15	7	0	2.420831	-0.744465	-0.000004
16	6	0	1.264091	-1.355851	-0.000005
17	1	0	1.280173	-2.444176	-0.000009

Geometry and free energy for zwitterion (324)



Sum of electronic and thermal Free Energies = -711.149014 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-3.644227	1.081056	0.469811
2	6	0	-2.267361	1.263247	0.432154
3	6	0	-1.536573	0.147952	-0.022036
4	6	0	-2.002217	-1.111469	-0.364113
5	6	0	-3.411682	-1.217792	-0.282007
6	6	0	-4.210453	-0.139851	0.096922
7	1	0	-4.277022	1.890441	0.820008
8	1	0	-5.291982	-0.247418	0.131767
9	6	0	0.712874	-0.613754	0.393583
10	6	0	2.114054	-0.555946	0.266598
11	6	0	2.945249	-1.551479	0.838120
12	6	0	2.686953	0.526455	-0.448192
13	6	0	0.463635	1.359336	-0.844317
14	6	0	4.303749	-1.461655	0.695649
15	1	0	2.489771	-2.374952	1.375820
16	6	0	4.093457	0.592409	-0.579703
17	6	0	1.806164	1.486422	-1.011578
18	1	0	-0.259497	2.033098	-1.278896
19	6	0	4.878345	-0.381814	-0.017635
20	1	0	4.947780	-2.218633	1.125349
21	1	0	4.536655	1.415828	-1.127448
22	1	0	2.195493	2.311431	-1.594349
23	1	0	5.955745	-0.330062	-0.120321
24	7	0	-0.065199	0.317662	-0.127138
25	1	0	0.194723	-1.420739	0.896534
26	6	0	-4.066172	-2.538710	-0.622665
27	1	0	-3.645677	-3.337632	-0.006892
28	1	0	-5.148478	-2.514622	-0.471632
29	1	0	-3.868025	-2.803838	-1.664410
30	6	0	-1.667688	2.559386	0.931697
31	1	0	-0.700714	2.406472	1.416921
32	1	0	-1.523600	3.290488	0.130327
33	1	0	-2.337422	3.013732	1.663468

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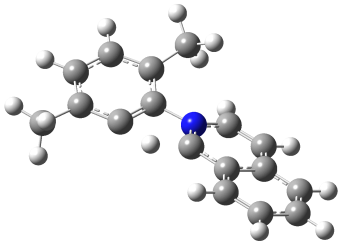
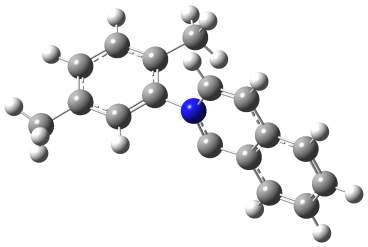
Geometry and free energy for $TS_{protonshift}$



Sum of electronic and thermal Free Energies = -711.133741 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-3.780294	-0.908987	-0.168947
2	6	0	-2.442000	-1.311097	-0.191252
3	6	0	-1.523552	-0.277954	0.033217
4	6	0	-1.820870	1.067794	0.160013
5	6	0	-3.175431	1.418596	0.154268
6	6	0	-4.144696	0.420275	0.020808
7	1	0	-4.549288	-1.656483	-0.336125
8	1	0	-5.199762	0.680462	0.030642
9	6	0	0.648721	0.615111	-0.173478
10	6	0	2.061679	0.558782	-0.120071
11	6	0	2.836634	1.715751	-0.386542
12	6	0	2.714696	-0.662844	0.190630
13	6	0	0.546817	-1.680279	0.433851
14	6	0	4.205424	1.650633	-0.349493
15	1	0	2.321172	2.639793	-0.620416
16	6	0	4.127422	-0.705469	0.221622
17	6	0	1.899344	-1.787604	0.490598
18	1	0	-0.109687	-2.488624	0.707655
19	6	0	4.851623	0.429850	-0.044955
20	1	0	4.799632	2.532572	-0.554920
21	1	0	4.626284	-1.638351	0.458881
22	1	0	2.347891	-2.726140	0.790627
23	1	0	5.934499	0.394971	-0.020813
24	7	0	-0.041492	-0.496124	0.065993
25	1	0	-0.360720	1.445583	-0.103360
26	6	0	-3.587253	2.865199	0.292618
27	1	0	-3.250323	3.268736	1.250728
28	1	0	-3.124144	3.469342	-0.491366
29	1	0	-4.670667	2.987885	0.228955
30	6	0	-2.131114	-2.749620	-0.542363
31	1	0	-1.262694	-2.833322	-1.199217
32	1	0	-1.950878	-3.370392	0.340567
33	1	0	-2.983779	-3.181989	-1.066948

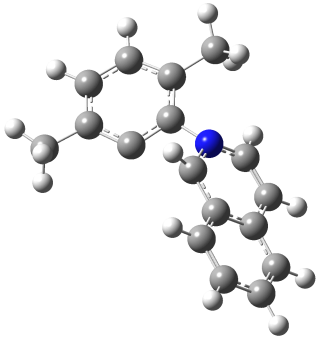
Geometry and free energy for carbene (325)



Sum of electronic and thermal Free Energies = -711.191244 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-3.487426	1.203239	-0.658733
2	6	0	-2.100626	1.258646	-0.524549
3	6	0	-1.475183	0.129286	0.006559
4	6	0	-2.182902	-1.002508	0.378136
5	6	0	-3.569653	-1.047344	0.239477
6	6	0	-4.210076	0.076797	-0.279571
7	1	0	-4.008067	2.057824	-1.077740
8	1	0	-5.288522	0.069394	-0.397554
9	6	0	0.710327	-0.591279	-0.666833
10	6	0	2.128215	-0.479474	-0.395793
11	6	0	3.017386	-1.197303	-1.227913
12	6	0	2.667453	0.309454	0.650129
13	6	0	0.429792	0.925836	1.230796
14	6	0	4.377497	-1.134717	-1.030720
15	1	0	2.588207	-1.795581	-2.023361
16	6	0	4.063867	0.364384	0.842714
17	6	0	1.751564	1.025541	1.480335
18	1	0	-0.329327	1.427790	1.816686
19	6	0	4.900931	-0.346462	0.013464
20	1	0	5.050462	-1.689282	-1.673585
21	1	0	4.466700	0.971327	1.646520
22	1	0	2.106135	1.636231	2.301148
23	1	0	5.973567	-0.301730	0.163789
24	7	0	-0.036514	0.137810	0.183566
25	1	0	-1.636468	-1.855002	0.768046
26	6	0	-4.337097	-2.287043	0.618554
27	1	0	-4.227049	-3.056867	-0.149788
28	1	0	-3.969649	-2.704105	1.558059
29	1	0	-5.400469	-2.072120	0.729856
30	6	0	-1.310257	2.463440	-0.962369
31	1	0	-0.923949	3.026199	-0.107898
32	1	0	-0.452555	2.164842	-1.569580
33	1	0	-1.936298	3.133442	-1.551652

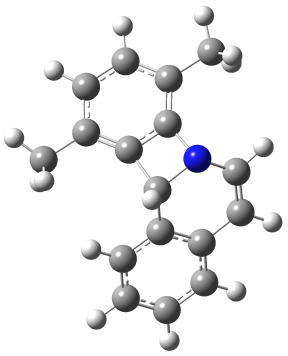
Geometry and free energy for $TS_{ringclosing}$



Sum of electronic and thermal Free Energies = -711.133298 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	3.838613	-0.513412	0.013935
2	6	0	2.640486	-1.186192	0.244523
3	6	0	1.495834	-0.400499	0.107209
4	6	0	1.454332	0.970053	-0.196405
5	6	0	2.689508	1.620330	-0.311480
6	6	0	3.861001	0.854367	-0.264716
7	1	0	4.773068	-1.061250	0.082042
8	1	0	4.819023	1.333900	-0.448671
9	6	0	-0.555136	0.270527	0.684110
10	6	0	-1.951728	0.344285	0.378269
11	6	0	-2.725731	1.437995	0.808682
12	6	0	-2.552010	-0.707430	-0.352643
13	6	0	-0.426292	-1.846796	-0.433746
14	6	0	-4.067140	1.499152	0.502619
15	1	0	-2.246257	2.234075	1.367624
16	6	0	-3.925063	-0.626221	-0.647968
17	6	0	-1.740863	-1.827966	-0.745013
18	1	0	0.251930	-2.621940	-0.762828
19	6	0	-4.665791	0.460225	-0.231698
20	1	0	-4.662438	2.344251	0.825348
21	1	0	-4.392715	-1.427840	-1.208607
22	1	0	-2.173872	-2.640116	-1.313284
23	1	0	-5.721754	0.513142	-0.469327
24	7	0	0.150792	-0.837009	0.297055
25	1	0	-0.160385	0.841596	1.507116
26	6	0	2.755364	3.110043	-0.546691
27	1	0	2.254191	3.646999	0.262497
28	1	0	3.786678	3.463271	-0.606138
29	1	0	2.242545	3.374550	-1.474255
30	6	0	2.604422	-2.639131	0.643858
31	1	0	1.799507	-2.833952	1.356645
32	1	0	2.448036	-3.291611	-0.220855
33	1	0	3.548066	-2.931981	1.106229

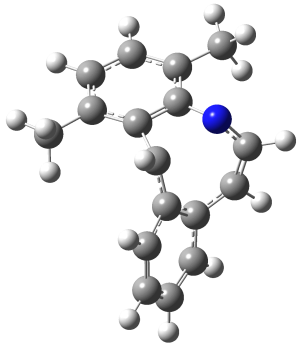
Geometry and free energy for intermediate (326)



Sum of electronic and thermal Free Energies = -711.194186 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	3.448168	0.339680	-0.691527
2	6	0	2.782272	-0.826302	-0.279205
3	6	0	1.543601	-0.559512	0.273822
4	6	0	0.990725	0.706001	0.412170
5	6	0	1.651318	1.856902	0.032034
6	6	0	2.914810	1.621729	-0.541924
7	1	0	4.431560	0.236710	-1.140167
8	1	0	3.498829	2.471109	-0.880753
9	6	0	-0.239453	0.086857	1.075349
10	6	0	-1.584089	0.163844	0.396242
11	6	0	-2.233275	1.384464	0.263776
12	6	0	-2.198907	-1.014191	-0.056881
13	6	0	-0.198609	-2.346357	0.386974
14	6	0	-3.502412	1.455098	-0.305771
15	1	0	-1.747968	2.287708	0.620471
16	6	0	-3.474603	-0.931527	-0.621600
17	6	0	-1.479833	-2.291751	0.003529
18	1	0	0.390995	-3.255453	0.335144
19	6	0	-4.124445	0.291075	-0.745069
20	1	0	-4.002454	2.411651	-0.398970
21	1	0	-3.953153	-1.839116	-0.974262
22	1	0	-1.984198	-3.189961	-0.329821
23	1	0	-5.113514	0.335875	-1.185329
24	7	0	0.464024	-1.236548	0.917942
25	1	0	-0.333405	0.339950	2.136581
26	6	0	1.074300	3.238203	0.174478
27	1	0	0.314794	3.419826	-0.590865
28	1	0	0.599900	3.366435	1.150396
29	1	0	1.849303	3.998021	0.066829
30	6	0	3.349910	-2.210047	-0.420502
31	1	0	3.277687	-2.757868	0.522585
32	1	0	2.807202	-2.782376	-1.178031
33	1	0	4.399391	-2.171668	-0.714764

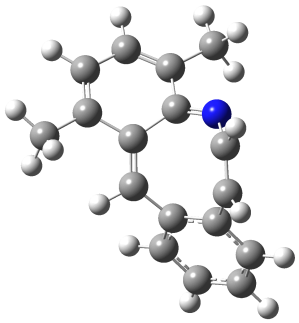
Geometry and free energy for $TS_{ringopening}$



Sum of electronic and thermal Free Energies = -711.143061 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	3.182474	0.441385	-0.875488
2	6	0	2.636985	-0.677731	-0.245415
3	6	0	1.471026	-0.418325	0.477487
4	6	0	0.878813	0.811982	0.518039
5	6	0	1.413832	1.939183	-0.099181
6	6	0	2.599002	1.713047	-0.800909
7	1	0	4.104144	0.322973	-1.436913
8	1	0	3.076746	2.542118	-1.312514
9	6	0	-0.386314	0.561858	1.249486
10	6	0	-1.555501	0.163881	0.546496
11	6	0	-2.747779	0.900198	0.797451
12	6	0	-1.612096	-0.905961	-0.409002
13	6	0	0.078720	-2.271023	0.753300
14	6	0	-3.846709	0.779117	-0.010888
15	1	0	-2.735468	1.635299	1.594939
16	6	0	-2.755845	-0.973045	-1.256477
17	6	0	-0.816707	-2.081713	-0.282151
18	1	0	0.119209	-3.260272	1.214047
19	6	0	-3.829850	-0.142780	-1.082043
20	1	0	-4.717409	1.400917	0.157518
21	1	0	-2.781682	-1.743638	-2.019181
22	1	0	-1.195844	-2.961322	-0.794090
23	1	0	-4.688286	-0.221997	-1.738550
24	7	0	0.756270	-1.280789	1.354508
25	1	0	-0.571538	1.132958	2.160600
26	6	0	0.736091	3.279706	-0.034149
27	1	0	0.661658	3.633458	0.997872
28	1	0	1.285894	4.025090	-0.609494
29	1	0	-0.280407	3.218248	-0.433087
30	6	0	3.254580	-2.045274	-0.300857
31	1	0	3.325848	-2.474820	0.701826
32	1	0	2.645289	-2.726096	-0.902204
33	1	0	4.253617	-2.004420	-0.736531

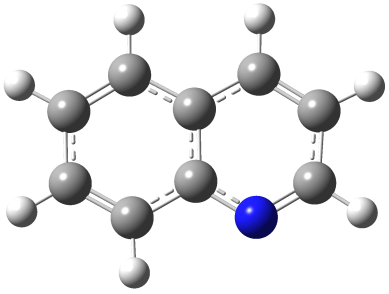
Geometry and free energy for benzoazocine (327)



Sum of electronic and thermal Free Energies = -711.178595 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	3.229846	-0.445655	-0.977060
2	6	0	2.181430	-1.271148	-0.791771
3	6	0	1.132659	-0.821279	0.147726
4	6	0	1.008795	0.654897	0.315881
5	6	0	2.271389	1.419963	0.293654
6	6	0	3.319786	0.863010	-0.343355
7	1	0	4.065744	-0.775109	-1.586309
8	1	0	4.251032	1.412581	-0.429989
9	6	0	-0.173968	1.295102	0.249188
10	6	0	-1.509652	0.747562	-0.088206
11	6	0	-2.168909	1.341184	-1.172394
12	6	0	-2.162081	-0.254689	0.643083
13	6	0	-0.356999	-1.445831	1.876066
14	6	0	-3.437129	0.930659	-1.556042
15	1	0	-1.670359	2.135504	-1.718224
16	6	0	-3.452431	-0.639514	0.263573
17	6	0	-1.553197	-0.857022	1.846657
18	1	0	-0.014539	-1.910478	2.797905
19	6	0	-4.084077	-0.066973	-0.831556
20	1	0	-3.923576	1.395999	-2.404865
21	1	0	-3.959310	-1.403678	0.842950
22	1	0	-2.153475	-0.874845	2.750808
23	1	0	-5.080002	-0.388242	-1.112362
24	7	0	0.488388	-1.714828	0.796962
25	1	0	-0.145187	2.381859	0.283717
26	6	0	2.319392	2.808248	0.865460
27	1	0	3.348245	3.167513	0.894834
28	1	0	1.740169	3.510651	0.258928
29	1	0	1.908886	2.832747	1.877562
30	6	0	2.101303	-2.661983	-1.341931
31	1	0	2.925964	-2.850586	-2.029919
32	1	0	2.135802	-3.393298	-0.531580
33	1	0	1.154944	-2.816002	-1.866030

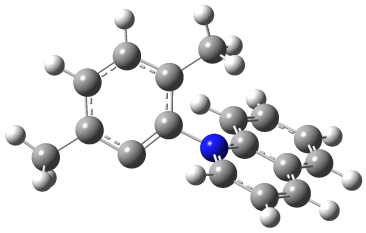
Geometry and free energy for quinoline (301b)



Sum of electronic and thermal Free Energies = -401.75446 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.417126	0.615772	0.000000
2	6	0	1.260889	1.350027	0.000000
3	6	0	0.000000	0.701207	0.000000
4	6	0	-0.044434	-0.718016	0.000000
5	6	0	1.168692	-1.452583	0.000000
6	6	0	2.372627	-0.800098	0.000000
7	1	0	3.377172	1.118162	0.000000
8	1	0	1.272387	2.433220	0.000000
9	6	0	-1.318609	-1.336093	0.000000
10	1	0	1.123878	-2.536436	0.000000
11	1	0	3.297482	-1.364278	0.000000
12	6	0	-2.438806	-0.553285	0.000000
13	6	0	-2.283570	0.855545	0.000000
14	1	0	-1.386235	-2.419036	0.000000
15	1	0	-3.432330	-0.983061	0.000000
16	1	0	-3.166880	1.488600	0.000000
17	7	0	-1.126995	1.469710	0.000000

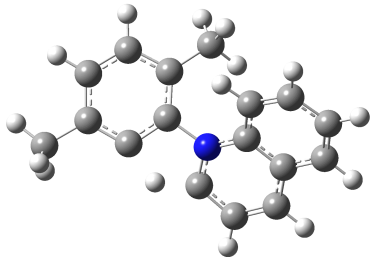
Geometry and free energy for quinoline zwitterion 328



Sum of electronic and thermal Free Energies = -711.147606 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.758562	-1.157685	1.150972
2	6	0	1.452005	-0.690214	1.182621
3	6	0	1.128533	0.230463	0.168098
4	6	0	1.933716	0.766391	-0.818843
5	6	0	3.251984	0.239214	-0.778632
6	6	0	3.644870	-0.703619	0.168587
7	1	0	3.092633	-1.862869	1.905462
8	1	0	0.459581	2.554290	0.729709
9	1	0	4.662459	-1.087085	0.166064
10	6	0	-2.202983	-2.149007	-0.980669
11	6	0	-1.121739	-1.386354	-0.622365
12	6	0	-1.331510	-0.062132	-0.177618
13	6	0	-2.641464	0.475929	-0.136178
14	6	0	-3.734025	-0.349085	-0.504081
15	6	0	-3.519507	-1.636852	-0.912493
16	1	0	-2.044026	-3.161713	-1.330545
17	1	0	-0.112441	-1.770647	-0.687341
18	6	0	-2.811348	1.827014	0.243044
19	1	0	-4.734485	0.065747	-0.462443
20	1	0	-4.354208	-2.265011	-1.197484
21	6	0	-1.720628	2.596571	0.546351
22	6	0	-0.448728	2.010004	0.507472
23	1	0	-3.812369	2.243028	0.274480
24	1	0	-1.810355	3.638078	0.820800
25	7	0	-0.273357	0.738498	0.192988
26	6	0	4.259725	0.727143	-1.796311
27	1	0	4.382691	1.810358	-1.714855
28	1	0	5.237998	0.255843	-1.670234
29	1	0	3.902970	0.525892	-2.809510
30	6	0	0.489641	-1.132107	2.258547
31	1	0	-0.064693	-0.287121	2.677083
32	1	0	-0.247202	-1.849220	1.883438
33	1	0	1.032327	-1.613104	3.073449

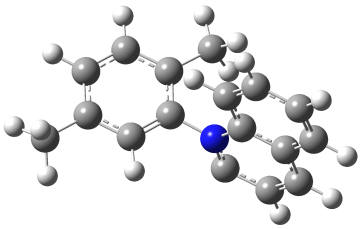
Geometry and free energy for $TS_{quinolinecarbene}$



Sum of electronic and thermal Free Energies = -711.124955 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.687515	-1.727417	0.466042
2	6	0	-1.364186	-1.295949	0.603532
3	6	0	-1.112928	-0.019752	0.089982
4	6	0	-2.070317	0.886822	-0.343432
5	6	0	-3.384565	0.418811	-0.432558
6	6	0	-3.670458	-0.903489	-0.071557
7	1	0	-2.955506	-2.711245	0.838369
8	1	0	-1.163051	2.030663	0.053515
9	1	0	-4.686053	-1.280799	-0.154868
10	6	0	2.702738	-1.826891	-1.011816
11	6	0	1.480482	-1.262579	-0.743211
12	6	0	1.420231	0.004792	-0.127088
13	6	0	2.614570	0.724094	0.116941
14	6	0	3.857526	0.094489	-0.135193
15	6	0	3.902726	-1.163085	-0.677154
16	1	0	2.745695	-2.793699	-1.498894
17	1	0	0.564617	-1.760690	-1.028349
18	6	0	2.520093	2.084951	0.507100
19	1	0	4.768245	0.641673	0.080504
20	1	0	4.854785	-1.637105	-0.880720
21	6	0	1.296996	2.696729	0.558788
22	6	0	0.116959	1.940281	0.401219
23	1	0	3.434965	2.635364	0.703596
24	1	0	1.213288	3.756737	0.762318
25	7	0	0.223917	0.630532	0.167178
26	6	0	-4.489351	1.333575	-0.905599
27	1	0	-4.459264	2.278497	-0.358465
28	1	0	-4.364793	1.571346	-1.965270
29	1	0	-5.475303	0.883642	-0.770451
30	6	0	-0.396658	-2.140665	1.401570
31	1	0	0.061736	-2.936164	0.808396
32	1	0	0.410090	-1.544789	1.831076
33	1	0	-0.934924	-2.615460	2.223604

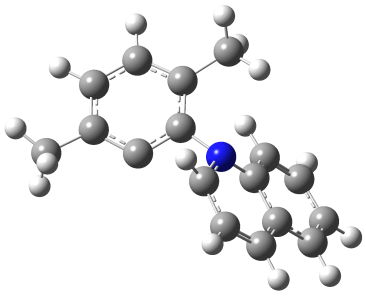
Geometry and free energy for quinoline carbene 329



Sum of electronic and thermal Free Energies = -711.187546 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.821911	0.068886	1.546610
2	6	0	1.500865	-0.339621	1.367960
3	6	0	1.038748	-0.413605	0.054534
4	6	0	1.839341	-0.100247	-1.031933
5	6	0	3.158049	0.311192	-0.843301
6	6	0	3.635373	0.389694	0.464727
7	1	0	3.221922	0.127802	2.553344
8	1	0	1.424973	-0.192379	-2.030849
9	1	0	4.660795	0.698081	0.640221
10	6	0	-2.017274	2.440712	0.195723
11	6	0	-1.003633	1.510130	0.137226
12	6	0	-1.312946	0.159973	-0.125015
13	6	0	-2.651278	-0.223527	-0.330622
14	6	0	-3.666974	0.754316	-0.267258
15	6	0	-3.358638	2.067251	-0.006533
16	1	0	-1.774449	3.476836	0.399821
17	1	0	0.024223	1.811094	0.291438
18	6	0	-2.918952	-1.597810	-0.598380
19	1	0	-4.693949	0.445211	-0.428515
20	1	0	-4.140926	2.814401	0.044235
21	6	0	-1.896955	-2.493143	-0.646234
22	6	0	-0.512872	-2.147108	-0.429518
23	1	0	-3.950072	-1.900447	-0.760274
24	1	0	-2.111958	-3.535790	-0.852406
25	7	0	-0.328823	-0.833529	-0.187394
26	6	0	4.027628	0.678508	-2.017521
27	1	0	3.901744	1.733583	-2.276062
28	1	0	5.081930	0.514808	-1.790458
29	1	0	3.768752	0.087826	-2.897502
30	6	0	0.610460	-0.705733	2.523662
31	1	0	-0.256614	-0.040943	2.582126
32	1	0	0.232326	-1.724363	2.406973
33	1	0	1.155955	-0.640230	3.464906

Geometry and free energy for $TS_{quinolineringclosing}$



Sum of electronic and thermal Free Energies = -711.128667 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.870211	1.655390	0.107010
2	6	0	-1.570363	1.446206	0.572516
3	6	0	-1.041956	0.186937	0.292062
4	6	0	-1.742371	-0.889963	-0.286947
5	6	0	-3.076831	-0.662291	-0.632955
6	6	0	-3.596753	0.633337	-0.498796
7	1	0	-3.335600	2.623735	0.263683
8	1	0	-0.784992	-1.833083	1.635772
9	1	0	-4.603347	0.843774	-0.851228
10	6	0	2.788925	1.808272	-0.973059
11	6	0	1.573732	1.411482	-0.450817
12	6	0	1.438769	0.126915	0.099524
13	6	0	2.525145	-0.774756	0.034191
14	6	0	3.753701	-0.334774	-0.489646
15	6	0	3.894924	0.946500	-0.976627
16	1	0	2.882211	2.802574	-1.393539
17	1	0	0.724834	2.078157	-0.480960
18	6	0	2.315741	-2.138290	0.426345
19	1	0	4.583291	-1.032766	-0.519224
20	1	0	4.842478	1.279163	-1.381044
21	6	0	1.101431	-2.559356	0.856960
22	6	0	0.034841	-1.624724	0.970664
23	1	0	3.151825	-2.826783	0.366248
24	1	0	0.924696	-3.584117	1.154032
25	7	0	0.250239	-0.302072	0.672679
26	6	0	-3.931820	-1.776714	-1.186400
27	1	0	-3.903679	-2.644421	-0.523347
28	1	0	-4.971528	-1.464751	-1.303316
29	1	0	-3.557862	-2.103223	-2.159792
30	6	0	-0.867781	2.491572	1.404495
31	1	0	-1.523058	2.831254	2.209298
32	1	0	0.046171	2.099980	1.853624
33	1	0	-0.601854	3.370564	0.809926

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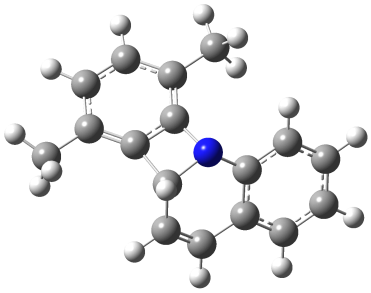
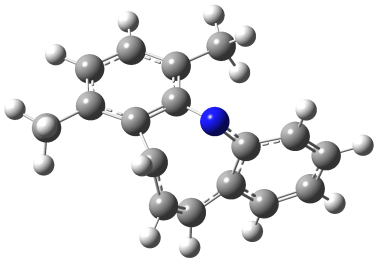
Geometry and free energy for quinoline azetidine 330



Sum of electronic and thermal Free Energies = -711.192771 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.602715	1.859380	-0.582675
2	6	0	-1.269474	1.839422	-0.138110
3	6	0	-0.884677	0.592221	0.327711
4	6	0	-1.710489	-0.523445	0.341749
5	6	0	-3.025217	-0.504902	-0.073186
6	6	0	-3.448337	0.749212	-0.548657
7	1	0	-2.995499	2.795200	-0.968757
8	1	0	-0.742516	-1.749198	1.916347
9	1	0	-4.466091	0.857306	-0.908595
10	6	0	3.623202	1.201515	0.201972
11	6	0	2.326116	1.125729	0.702238
12	6	0	1.547653	0.000407	0.457437
13	6	0	2.076647	-1.077774	-0.271321
14	6	0	3.385369	-0.994914	-0.745810
15	6	0	4.157959	0.139423	-0.519791
16	1	0	4.219409	2.085969	0.393014
17	1	0	1.910356	1.933392	1.292860
18	6	0	1.236106	-2.254256	-0.525501
19	1	0	3.792851	-1.828170	-1.309059
20	1	0	5.170505	0.192136	-0.900556
21	6	0	0.022665	-2.393814	0.009338
22	6	0	-0.564686	-1.353678	0.910650
23	1	0	1.641629	-3.025565	-1.172186
24	1	0	-0.581126	-3.273466	-0.188196
25	7	0	0.221658	-0.066587	0.951844
26	6	0	-3.916920	-1.716050	-0.062583
27	1	0	-3.647834	-2.401266	-0.871052
28	1	0	-3.824431	-2.262270	0.878666
29	1	0	-4.961926	-1.433668	-0.195142
30	6	0	-0.385712	3.055104	-0.168467
31	1	0	-0.066257	3.331845	0.840231
32	1	0	0.513999	2.879087	-0.761671
33	1	0	-0.919614	3.903280	-0.598779

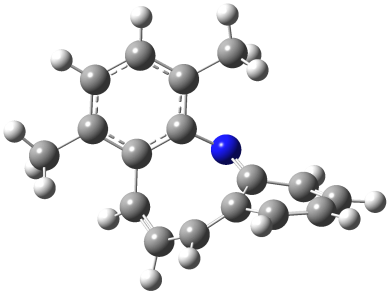
Geometry and free energy for $TS_{quinolineringopening}$



Sum of electronic and thermal Free Energies = -711.145699 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.169604	2.035077	-0.655468
2	6	0	-0.906732	1.811005	-0.105633
3	6	0	-0.751287	0.552982	0.480847
4	6	0	-1.721353	-0.411760	0.444615
5	6	0	-2.988294	-0.198991	-0.090232
6	6	0	-3.185595	1.070537	-0.637882
7	1	0	-2.375705	3.002142	-1.103972
8	1	0	-1.476077	-2.160824	1.787997
9	1	0	-4.147945	1.311400	-1.077217
10	6	0	3.830085	0.539412	0.448470
11	6	0	2.675037	0.482863	1.185707
12	6	0	1.497076	-0.082056	0.629944
13	6	0	1.613862	-0.849320	-0.573401
14	6	0	2.821683	-0.757363	-1.319004
15	6	0	3.892512	-0.052947	-0.835719
16	1	0	4.697734	1.056193	0.841710
17	1	0	2.590562	0.964372	2.152789
18	6	0	0.758570	-1.970276	-0.772144
19	1	0	2.893812	-1.291605	-2.260552
20	1	0	4.806065	0.013923	-1.414172
21	6	0	-0.234416	-2.401384	0.081491
22	6	0	-1.024006	-1.619402	0.955788
23	1	0	1.121690	-2.693319	-1.497860
24	1	0	-0.378055	-3.478721	0.136774
25	7	0	0.313481	0.056537	1.272651
26	6	0	-4.038798	-1.274590	-0.113852
27	1	0	-4.234962	-1.656969	0.891280
28	1	0	-4.976147	-0.896296	-0.523001
29	1	0	-3.714729	-2.120093	-0.727536
30	6	0	0.190876	2.836689	-0.097098
31	1	0	0.586942	2.966671	0.913995
32	1	0	1.027660	2.524937	-0.729510
33	1	0	-0.172906	3.799582	-0.457849

Geometry and free energy for quinoline azocine 331



Sum of electronic and thermal Free Energies = -711.176878 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.440367	1.952022	0.616013
2	6	0	-1.162588	1.855899	0.081542
3	6	0	-0.751142	0.613897	-0.438309
4	6	0	-1.602534	-0.489757	-0.405133
5	6	0	-2.905507	-0.366042	0.111862
6	6	0	-3.307539	0.862283	0.620509
7	1	0	-2.771017	2.902648	1.021749
8	1	0	-1.780095	-2.356753	-1.552570
9	1	0	-4.305809	0.969278	1.030874
10	6	0	3.947972	0.472905	-0.400296
11	6	0	2.849365	0.505108	-1.176970
12	6	0	1.553329	0.102602	-0.615808
13	6	0	1.641291	-0.831114	0.538700
14	6	0	2.803199	-0.673735	1.413565
15	6	0	3.906633	-0.053554	0.957997
16	1	0	4.885580	0.869556	-0.773383
17	1	0	2.846157	0.954727	-2.162525
18	6	0	0.899863	-1.958922	0.602150
19	1	0	2.780171	-1.145430	2.390091
20	1	0	4.793701	0.017086	1.575549
21	6	0	-0.065479	-2.453064	-0.381500
22	6	0	-1.136741	-1.813796	-0.865018
23	1	0	1.157076	-2.664008	1.391679
24	1	0	0.098560	-3.482648	-0.691744
25	7	0	0.493727	0.613345	-1.113575
26	6	0	-3.833374	-1.553604	0.138361
27	1	0	-4.069140	-1.897705	-0.873018
28	1	0	-3.381972	-2.395422	0.669680
29	1	0	-4.770340	-1.297387	0.633164
30	6	0	-0.228822	3.034357	0.043310
31	1	0	0.681528	2.835031	0.615640
32	1	0	0.084305	3.243628	-0.982852
33	1	0	-0.710149	3.921078	0.456844

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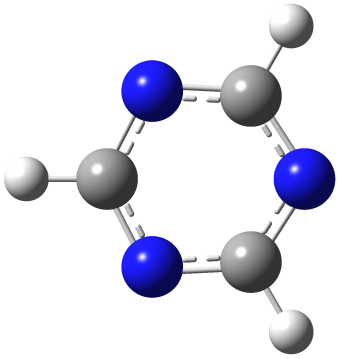
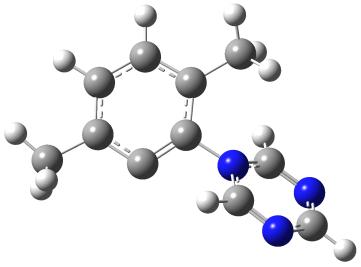
Geometry and free energy for triazine (301d)



Sum of electronic and thermal Free Energies = -280.291265 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.645485	1.118087	0.000000
2	6	0	-1.290578	0.000000	0.000000
3	6	0	0.645485	-1.118087	0.000000
4	7	0	1.366120	0.000000	0.000000
5	1	0	-2.376376	0.000000	0.000000
6	1	0	1.187790	2.058726	0.000000
7	1	0	1.187790	-2.058726	0.000000
8	7	0	-0.683171	1.183299	0.000000
9	7	0	-0.683171	-1.183299	0.000000

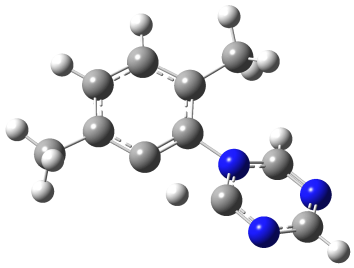
Geometry and free energy for triazine zwitterion 332



Sum of electronic and thermal Free Energies = -589.673566 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.575454	-1.131604	-0.732944
2	6	0	-3.617690	-0.676074	0.077730
3	6	0	-1.897588	0.574972	0.781456
4	7	0	-1.061921	-0.116784	-0.005488
5	1	0	-4.677905	-0.901740	0.106394
6	1	0	-0.861153	-1.689753	-1.324643
7	1	0	-1.459963	1.347472	1.401392
8	6	0	2.523329	-0.868768	0.133902
9	6	0	1.124681	-1.086082	0.108735
10	6	0	0.404611	0.089278	-0.013750
11	6	0	0.867669	1.411362	-0.163600
12	6	0	2.249383	1.536933	-0.122567
13	6	0	3.063612	0.412637	0.042256
14	1	0	2.696384	2.518266	-0.244770
15	1	0	4.141285	0.551822	0.074170
16	6	0	0.001658	2.623865	-0.421576
17	1	0	-0.881632	2.384024	-1.019674
18	1	0	-0.339446	3.099074	0.503211
19	1	0	0.573139	3.372825	-0.971059
20	6	0	3.447570	-2.057879	0.264681
21	1	0	3.244945	-2.781544	-0.528482
22	1	0	4.500346	-1.769603	0.214541
23	1	0	3.273908	-2.570548	1.214117
24	7	0	-3.189464	0.326706	0.842922
25	7	0	-2.857272	-1.428797	-0.716167

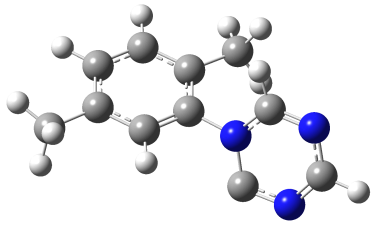
Geometry and free energy for $TS_{triazinecarbene}$



Sum of electronic and thermal Free Energies = -589.658644 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.048308	-1.009113	0.062419
2	6	0	2.447514	-0.927683	0.080660
3	6	0	3.064297	0.324408	0.056717
4	6	0	2.317125	1.497399	-0.037890
5	6	0	0.923765	1.478218	-0.075275
6	1	0	4.148115	0.395279	0.083022
7	1	0	-0.217343	-1.804490	-0.291802
8	1	0	2.826465	2.452587	-0.111618
9	6	0	-1.427517	-1.322221	-0.344995
10	6	0	-2.057715	0.803892	0.413843
11	6	0	-3.599969	-0.762677	-0.023155
12	1	0	-1.768433	1.772667	0.796726
13	1	0	-4.646604	-1.045673	-0.073203
14	6	0	3.278004	-2.187426	0.121921
15	1	0	4.347892	-1.970190	0.110136
16	1	0	3.051352	-2.764707	1.021346
17	1	0	3.043843	-2.823317	-0.735257
18	6	0	0.175247	2.773318	-0.286499
19	1	0	-0.658554	2.658642	-0.983687
20	1	0	-0.213910	3.189691	0.647490
21	1	0	0.852767	3.515795	-0.708612
22	7	0	-1.103132	-0.036901	0.008791
23	6	0	0.366648	0.195769	0.021797
24	7	0	-3.335136	0.476604	0.387409
25	7	0	-2.701708	-1.691073	-0.352171

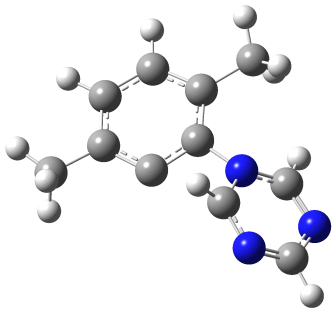
Geometry and free energy for triazine carbene 333



Sum of electronic and thermal Free Energies = -589.71606 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.603222	-0.965505	-1.086568
2	6	0	3.622363	-0.622972	0.034321
3	6	0	1.817542	0.229809	1.009857
4	7	0	1.079917	-0.225356	-0.023036
5	1	0	4.700051	-0.763642	0.052345
6	1	0	-0.815981	-2.009543	0.166592
7	1	0	1.292383	0.744273	1.810148
8	6	0	-2.593027	-0.782519	0.103742
9	6	0	-1.217119	-1.004311	0.094435
10	6	0	-0.337521	0.060286	-0.022658
11	6	0	-0.767937	1.381943	-0.155573
12	6	0	-2.146888	1.589229	-0.141180
13	6	0	-3.041036	0.532873	-0.008449
14	1	0	-2.525494	2.599718	-0.249828
15	1	0	-4.106866	0.734294	-0.004235
16	6	0	-3.551754	-1.938831	0.211259
17	1	0	-3.540341	-2.533717	-0.705372
18	1	0	-3.277926	-2.599006	1.036476
19	1	0	-4.571126	-1.588690	0.375000
20	6	0	0.193911	2.526674	-0.346291
21	1	0	0.678886	2.816898	0.589919
22	1	0	0.978553	2.269625	-1.061347
23	1	0	-0.336587	3.400531	-0.723722
24	7	0	3.108549	0.061041	1.078563
25	7	0	2.959236	-1.137229	-0.976006

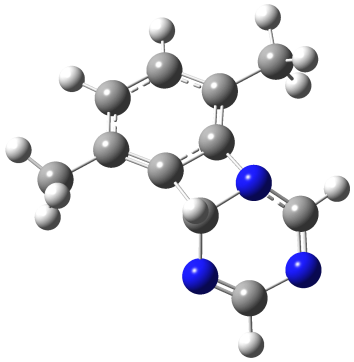
Geometry and free energy for $TS_{triazineringclosing}$



Sum of electronic and thermal Free Energies = -589.664162 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.395181	-1.005227	0.762582
2	6	0	3.417994	-0.865329	-0.224218
3	6	0	2.030251	0.875770	-0.489648
4	7	0	1.091445	0.226339	0.201326
5	1	0	4.367395	-1.329834	-0.470051
6	1	0	0.818359	-1.322834	1.612802
7	1	0	1.746131	1.825351	-0.929839
8	6	0	-2.223070	-1.084525	-0.139734
9	6	0	-0.826002	-0.974285	-0.062392
10	6	0	-0.334784	0.327620	0.072399
11	6	0	-1.062826	1.518638	0.110716
12	6	0	-2.435592	1.350504	-0.044439
13	6	0	-2.998929	0.078837	-0.176861
14	1	0	-3.078178	2.224834	-0.037394
15	1	0	-4.075236	-0.001719	-0.304753
16	6	0	-2.876540	-2.442515	-0.223575
17	1	0	-3.965006	-2.365309	-0.256626
18	1	0	-2.538064	-2.975321	-1.115101
19	1	0	-2.599528	-3.052192	0.639711
20	6	0	-0.445664	2.876060	0.330448
21	1	0	-1.185183	3.567203	0.736267
22	1	0	0.390754	2.828763	1.032282
23	1	0	-0.076191	3.308036	-0.604728
24	7	0	3.235345	0.389278	-0.686208
25	7	0	2.581015	-1.564227	0.514276

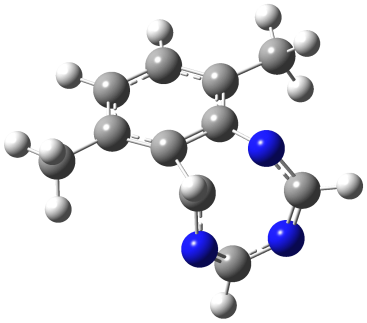
Geometry and free energy for triazine azetidine 334



Sum of electronic and thermal Free Energies = -589.726798 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.013238	-0.875532	0.671307
2	6	0	2.974637	-0.828502	-0.520099
3	6	0	2.157539	1.218823	0.038808
4	7	0	1.072252	0.630426	0.605331
5	1	0	3.756591	-1.316633	-1.096415
6	1	0	1.117332	-1.217995	1.705526
7	1	0	2.134781	2.303817	-0.050933
8	6	0	-1.644852	-1.362461	-0.009447
9	6	0	-0.444198	-0.728861	0.236875
10	6	0	-0.311885	0.655065	0.227490
11	6	0	-1.329125	1.552611	-0.024923
12	6	0	-2.547537	0.908663	-0.301899
13	6	0	-2.701537	-0.478423	-0.296519
14	1	0	-3.413118	1.525038	-0.523443
15	1	0	-3.679635	-0.892373	-0.518263
16	6	0	-1.808907	-2.855988	-0.012393
17	1	0	-1.416221	-3.280801	-0.939549
18	1	0	-1.259862	-3.311811	0.813613
19	1	0	-2.860057	-3.133726	0.071535
20	6	0	-1.152314	3.043982	-0.015248
21	1	0	-0.583186	3.362747	0.861314
22	1	0	-0.611332	3.380420	-0.904105
23	1	0	-2.118401	3.548949	0.001388
24	7	0	3.188924	0.557120	-0.364807
25	7	0	1.982075	-1.539533	-0.152580

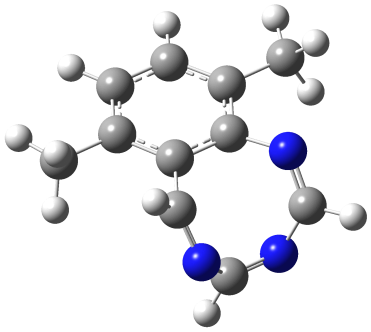
Geometry and free energy for $TS_{triazineringopening}$



Sum of electronic and thermal Free Energies = -589.693727 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.751609	-1.319027	0.868952
2	6	0	2.062167	-1.215380	-1.037101
3	6	0	2.364281	0.665363	0.249009
4	7	0	1.263768	0.556844	1.030783
5	1	0	2.367096	-1.732740	-1.941520
6	1	0	0.820054	-1.784933	1.850854
7	1	0	3.182204	1.272799	0.642817
8	6	0	-1.788816	-0.976480	0.028081
9	6	0	-0.512994	-0.626091	0.442340
10	6	0	-0.029318	0.652202	0.428496
11	6	0	-0.760130	1.746586	-0.018387
12	6	0	-2.052988	1.417259	-0.438619
13	6	0	-2.553920	0.110455	-0.412290
14	1	0	-2.698805	2.212847	-0.796651
15	1	0	-3.568332	-0.067207	-0.753204
16	6	0	-2.293643	-2.392043	0.035044
17	1	0	-2.310842	-2.795796	1.050424
18	1	0	-3.303751	-2.447697	-0.371095
19	1	0	-1.645065	-3.036357	-0.563488
20	6	0	-0.195560	3.136865	-0.038736
21	1	0	0.302531	3.361014	0.907856
22	1	0	0.548297	3.245513	-0.833233
23	1	0	-0.979867	3.875893	-0.204644
24	7	0	2.612781	0.019653	-0.858196
25	7	0	1.458072	-1.905295	-0.119565

Geometry and free energy for triazine azocine 335



Sum of electronic and thermal Free Energies = -589.754073 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.931685	-1.538401	-0.723808
2	6	0	-2.327737	-0.727156	0.934183
3	6	0	-2.171035	1.221845	-0.277150
4	7	0	-1.039918	1.365125	-0.833811
5	1	0	-2.532594	-1.260405	1.861585
6	1	0	-0.788883	-2.229469	-1.556257
7	1	0	-3.025438	1.750548	-0.697970
8	6	0	1.440069	-1.314111	-0.008660
9	6	0	0.224945	-0.689964	-0.333909
10	6	0	0.108921	0.708348	-0.336339
11	6	0	1.209177	1.507120	0.016733
12	6	0	2.392691	0.874190	0.375263
13	6	0	2.513897	-0.512849	0.358469
14	1	0	3.246199	1.480929	0.659381
15	1	0	3.455907	-0.976055	0.629952
16	6	0	1.562503	-2.816847	-0.033845
17	1	0	0.824114	-3.288964	0.619021
18	1	0	1.408097	-3.211561	-1.042284
19	1	0	2.553753	-3.125384	0.297374
20	6	0	1.083552	3.004857	0.000325
21	1	0	0.741720	3.348924	-0.978413
22	1	0	0.346275	3.344838	0.732017
23	1	0	2.040291	3.474489	0.229498
24	7	0	-2.446020	0.535819	0.910867
25	7	0	-2.071381	-1.559528	-0.160125

Supplementary Information for Chapter 4

General Experimental Information

"^{1}H and ^{13}C NMR spectra were measured on Bruker Avance 500 or 400 spectrometers at 500 or 400 MHz, respectively. ^{1}H NMR chemical shifts for spectra in $CDCl_3$ are referenced to TMS (δ 0.00 ppm). ^{1}H NMR chemical shifts in C_6D_6 are referenced to CHD_5 (δ 7.16 ppm). Non-first order doublets, triplets and multiplets in ^{1}H NMR spectra are identified as such by the designation "nfod", "nfot", and "nfom". The following format is used for reporting resonances: the chemical shift in ppm [multiplicity, coupling constant(s) (Hz), integral, and assignment]. ^{1}H NMR assignments are designated by the neighboring atoms, e.g., C*Ha*Hb. Analysis of coupling constants was guided by methods we have reported earlier.[130,131] ^{13}C NMR chemical shifts for spectra recorded in $CDCl_3$ are referenced to the carbon" in TMS (δ 0.00 ppm).

Infrared spectra were collected on a Nicolet iS5 spectrometer as thin films.

HRMS were collected on either i) a Thermo Orbitrap Velos in the positive electron spray ionization (ESI) mode [external standard (Pierce™ LTQ); mass accuracy < 3 ppm; sample introduction as a dilute solution in methanol].

"MPLC refers to medium pressure liquid chromatography (25-200 psi) using dry-packed columns of silica gel (25-35 μm, 60 Å pore size). A Waters HPLC pump (M6000) was used to provide flow rates of ca. 6 mL•min^{-1}, A Waters R401 differential refractive index detector and a Gilson 116 UV detector were used to monitor the contents of the eluent. Flash chromatography was carried out on E. Merck silica gel (230-400 mesh). Thin layer chromatography was carried out on plastic-backed plates of silica gel. These were visualized by UV detection and, then, a solution of basic potassium permanganate. Reported reaction temperatures are those of the temperature of the external heating or cooling bath that was used. HDDA reactions were routinely performed in a threaded vial or culture tube fitted with an inert, Teflon®-lined cap."

General Experimental Procedure A: Synthesis of Thioamide 406

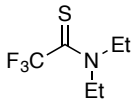
With the exception of **406e**, each trifluoroacetamide (1 equiv) was added to a slurry of 2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane (Lawesson's reagent, 0.7 equiv) in toluene ([Lawesson's] = 0.5 M). This mixture was heated with stirring in a

screw-capped culture tube in an oil bath held at ca. 110 °C. After ca. 4 h the mixture was cooled to ambient temperature and eluted through a silica gel plug (11:1 hexanes:EtOAc). The effluent was concentrated to provide the thioamide as a yellow oil or solid (60–90%), which was used for characterization and subsequent benzyne trapping reactions. The typical scale of the reaction was 2–5 mmol.

General Experimental Procedure B: Synthesis of Dihydrobenzothiazole Derivatives

A solution of polyyne substrate **226** and thioamide **406** (3 equiv) in benzene ([polyyne] = 0.01–0.02 M) was heated in a screw-capped culture tube in an oil bath held at ca. 85 °C. After 16 h the solution was cooled and passed through a plug of silica gel (EtOAc). The effluent was concentrated and the resulting residue was purified by MPLC to give the indicated product(s). The typical scale of the reaction was 0.1–1 mmol.

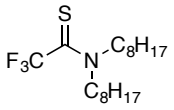
***N*,*N*-Diethyl-2,2,2-trifluoroethanethioamide (406a)**



Prepared following General Experimental Procedure A. Because of its volatility, thioamide **406a** (71%) was used as a solution in toluene obtained by initial elution of the reaction mixture through the silica gel plug. The titer of the solution was estimated by ^{1}H NMR analysis/integration of an aliquot of this solution. The NMR data were consistent with the reported data.[135]

[135] Nguyen, T.; Wakselman, C. Perfluorothioalkanoyl halides. Preparation from sulfides. *J. Fluor. Chem*., **1987**, *35*, 523-530.

2,2,2-Trifluoro-*N*,*N*-dioctylethanethioamide (406b)



Prepared following General Experimental Procedure A. Thioamide **406b** (1.43 g, 90%) was isolated as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.85 [nfot, *J* = 8.0 Hz, 2H, N(C*Ha*$_2$)(CHb$_2$)], 3.60 [nfot, *J* = 7.9 Hz, 2H, N(CHa$_2$)(C*Hb*$_2$)], 1.76–1.64 [m, 4H, N(CH_2C*H*$_2$)$_2$], 1.37–1.22 (m, 20H, (C*H*$_2$)$_5$), 0.889 (t, *J* = 6.8 Hz, 3H, CH_2C*Ha*$_3$), and 0.886 (t, *J* = 6.8 Hz, 3H, CH_2C*Hb*$_3$).

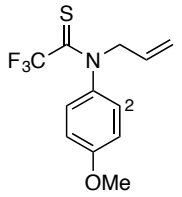
^{13}C NMR (125 MHz, $CDCl_3$): δ 180.8 (q, *J* = 34 Hz), 117.4 (q, *J*= 278 Hz), 54.5, 53.9 (q, *J* = 3.6 Hz), 31.8, 31.7, 29.16, 29.15, 29.09, 29.06, 28.5, 26.8, 26.7, 24.6, 22.63, 22.60, 14.08, and 14.06.

IR (neat): 2956, 2927, 2856, 1501, 1469, 1424, 1374, 1272, 1247, 1229, 1183, 1127, 1100, 1025, 743, and 723 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{18}H_{35}F_3NS^+$ [M+H$^+$] 354.2442, found 354.2438.

TLC: R_f 0.3 (10:1 hexanes:EtOAc).

***N*-Allyl-2,2,2-trifluoro-*N*-(4-methoxyphenyl)ethanethioamide (406c)**



Prepared following General Experimental Procedure A. Thioamide **406c** (1.23 g, 89%) was isolated as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09 (nfod, *J* = 8.9 Hz, 2H, *H2*), 6.90 (nfod, *J* = 8.7 Hz, 2H, *H3*), 5.95 (ddt, *J* = 16.7, 10.3, 6.4 Hz, 1H, CH_2=C*H*-CH_2), 5.27 (ddt, *J* = 10.2, 1.0, 1.0 Hz, 1H, C$H_a$$H_b$=CH-$CH_2$), 5.16 (ddt, *J* = 17.0, 1.2, 1.2 Hz, 1H, $CH_a$$H_b$=CH-$CH_2$), 4.77 (br ddd, *J* = 6.5, 1.2, 1.2 Hz, 2H, CH_2=CH-CH_2), and 3.84 (s, 3H, OCH_3).

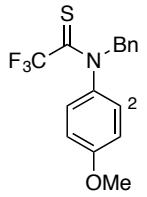
^{13}C NMR (125 MHz, $CDCl_3$): δ 183.6 (q, *J* = 34 Hz), 159.8, 135.4, 128.8, 128.0, 120.8, 117.2 (q, *J* = 279 Hz), 114.2, 61.9, and 55.5.

IR (neat): 3083, 3007, 2962, 2935, 2911, 2839, 1678, 1641, 1606, 1585, 1509, 1459, 1405, 1336, 1299, 1252, 1201, 1182, 1170, 1141, 1097, 1061, 1033, 993, and 969 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{12}H_{13}F_3NOS^+$ [$M+H^+$] 276.0670, found 276.0666.

TLC: R_f 0.4 (8:1 hexanes:EtOAc).

***N*-Benzyl-2,2,2-trifluoro-*N*-(4-methoxyphenyl)ethanethioamide (406d)**



Prepared following General Experimental Procedure A. Thioamide **406d** (0.66 g, 93%) was isolated as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30-7.26 (m, 3H, $C_6H_5CH_2$), 7.24-7.20 (m, 2H, $C_6H_5CH_2$), 6.89 (nfod, *J* = 9.0 Hz, 2H, *H2*), 6.80 (nfod, *J* = 9.0 Hz, 2H, *H3*), 5.48 (s, 2H, $C_6H_5CH_2$), and 3.79 (s, 3H, OCH_3).

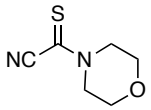
^{13}C NMR (125 MHz, $CDCl_3$): δ 184.4 (q, *J* = 34 Hz), 159.7, 134.9, 134.2, 129.1, 128.6, 128.3 (q, *J* = 1.2 Hz), 128.2, 117.4 (q, *J* = 280 Hz), 114.0, 62.1, and 55.4.

IR (neat): 3064, 3031, 3006, 2957, 2934, 2838, 1644, 1606, 1585, 1508, 1449, 1417, 1352, 1299, 1252, 1194, 1169, 1141, 1095, 1080, 1031, 1002, and 975 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{16}H_{15}F_3NOS^+$ $[M+H^+]$ 326.0826, found 326.0823.

TLC: R_f 0.3 (8:1 hexanes:EtOAc).

Morpholine-4-carbothioyl cyanide (406e)



To a stirred solution of precipitated sulfur (0.96 g, 3 equiv) and morpholine (2.6 mL, 30 mmol, 3 equiv) in dimethylformamide (5 mL) was added dropwise a solution of chloroacetonitrile (0.64 mL, 10 mmol, 1 equiv) in dimethylformamide (7 mL). The dark red solution was stirred at room temperature overnight. After 20 hours, the reaction mixture was quenched upon addition of water and the orange aqueous layer was extracted thrice with ethyl acetate. Precipitated sulfur was filtered from the combined organic layers, and the organic layers were concentrated under reduced pressure. The resulting crude orange oil was purified by flash column chromatography (hexanes/EtOAc = 5:1 to 3:1) to give **406e** as a yellow, foul smelling crystalline solid (52 mg, 3%).[136]

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.17 [nfot, J = 4.7 Hz, 2H, N(C*H*a_2)(CHb_2)], 4.09 [nfot, J = 4.4 Hz, 2H, N(CHa_2)(C*H*b_2)], 3.85 [nfot, J = 4.8 Hz, 2H, O(C*H*a_2)(CHb_2)], and 3.81 [nfod, J = 5.0 Hz, 2H, O(CHa_2)(C*H*b_2)].

^{13}C NMR (125 MHz, $CDCl_3$): δ 164.2, 111.5, 66.5, 65.8, 53.7, and 47.3.

IR (neat): 2986, 2866, 2210, 1605, 1551, 1511, 1486, 1461, 1440, 1421, 1301, 1245, 1155, 1116, 1066, 1028, 1007, and 986 cm^{-1}.

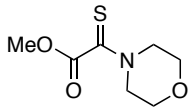
HRMS (ESI-TOF): Calculated for $C_6H_9N_2OS^+$ [M+H$^+$] 157.0436, found 157.0446.

TLC: R_f 0.5 (3:1 hexanes:EtOAc).

mp: 119-120 °C.

[136] Durton–Woitrin, F.; Merényi, R.; Viehe, H. G. Aminosulfuration of Captodative Methylene Compounds to form Thioamides with α-Captor Substituents. *Synthesis* **1985**, *1*, 79–80.

Methyl 2-morpholino-2-thioxoacetate (406f)



Prepared following General Experimental Procedure A. Thioamide **406f** (0.90 g, 69%) was isolated as a light yellow crystal.

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.18 [nfot, *J* = 4.8 Hz, 2H, N(C*Ha*$_2$)(CHb$_2$)], 3.90 (s, 3H, OC*H*$_3$), 3.83 [nfom, N(CHa$_2$)(C*Hb*$_2$)], 3.77 [nfom, 2H, O(C*Ha*$_2$)(CHb$_2$)], and 3.62 [nfom, 2H, O(CHa$_2$)(C*Hb*$_2$)].

^{13}C NMR (125 MHz, $CDCl_3$): δ 188.2, 164.0, 66.4, 66.0, 53.4, 52.5, and 46.9.

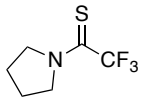
IR (neat): 2984, 2956, 2928, 2864, 1737, 1499, 1461, 1441, 1434, 1388, 1360, 1300, 1237, 1215, 1197, 1114, 1072, 1065, 1029, 1009, and 957 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_7H_{12}NO_3S^+$ [M+H$^+$] 190.0538, found 190.0533.

TLC: R_f 0.2 (2:1 hexanes:EtOAc).

mp: 81-84 °C.

2,2,2-Trifluoro-1-(pyrrolidin-1-yl)ethane-1-thione (406g)



Prepared following General Experimental Procedure A. Thioamide **406g** (0.48 g, 56%) was obtained as a yellow crystalline solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.86 (app tq, *J* = 7.0, 0.8 Hz, 4H, NC2H_2, NC5H_2), 2.15–2.09 (app tt, 2H, C3H_2 or C4H_2), and 2.06–2.00 (app tt, C3H_2 or C4H_2).

^{13}C NMR (125 MHz, $CDCl_3$): δ 178.9 (q, *J* = 36 Hz), 117.2 (q, *J* = 278 Hz), 55.5, 52.1 (q, *J* = 4.0 Hz), 26.7, and 23.4.

IR (neat): 2986, 2949, 2936, 2842, 1596, 1570, 1503, 1462, 1447, 1421, 1299, 1185, 1122, 1025, 1009, and 932 cm^{-1}.

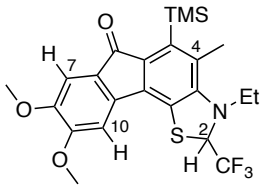
HRMS (ESI-TOF): Calculated for $C_6H_9F_3NS^+$ [M+H$^+$] 184.0408, found 184.0400.

TLC: R_f 0.2 (11:1 hexanes:EtOAc).

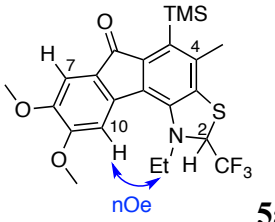
mp: 57–59 °C.

1-Ethyl-8,9-dimethoxy-4-methyl-2-(trifluoromethyl)-5-(trimethylsilyl)-1,2-dihydro-6*H*-fluoreno[4,3-*d*]thiazol-6-one (408') and

3-Ethyl-8,9-dimethoxy-4-methyl-2-(trifluoromethyl)-5-(trimethylsilyl)-2,3-dihydro-6*H*-fluoreno[3,4-*d*]thiazol-6-one (408)



5aa'



5aa

Prepared following General Experimental Procedure B. In order of elution (hexanes:EtOAc 11:1), the fluorenone derivatives **408'** (9.0 mg) and **408** (21.2 mg) were isolated in 20% and 48% yield and each as an amorphous orange foamy solid.

Compound 408'

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16 (s, 1H, *H7*), 6.89 (s, 1H, *H10*), 5.19 (q, *J* = 6.5 Hz, 0.5H, C*H*CF_3), 4.03 (s, 3H, C9OC*H*$_3$), 3.91 (s, 3H, C8OC*H*$_3$), 3.26 (dq, *J* = 14.1, 7.1 Hz, 1H, C*H*$_a$H$_b$$CH_3$), 3.04 (dq, *J* = 14.5, 7.3 Hz, 1H, CH_a*H*$_b$$CH_3$), 2.39 (s, 3H, ArC*H*$_3$), 1.30 (t, *J* = 7.2 Hz, 1H, CH_2C*H*$_3$), and 0.41 [s, 9H, Si(C*H*$_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 192.8, 154.3, 153.2, 149.3, 140.9, 137.9, 137.4, 135.7, 130.8 (d, *J* = 1.8 Hz), 127.1, 125.1, 123.3 (q, *J* = 280 Hz), 106.9, 104.6, 71.6 (q, *J* = 34 Hz), 56.4, 56.2, 50.01 (d, *J* = 8.1 Hz), 21.3, 13.6, and 2.7.

IR (neat): 2979, 2940, 2900, 2838, 1702, 1627, 1595, 1546, 1494, 1359, 1313, 1216, 1206, 1187, 1139, 1097, 1023, and 950 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{23}H_{27}F_3NO_3SSi^+$ [M+H$^+$] 482.1433, found 482.1429.

TLC: R_f 0.2 (11:1 hexanes:EtOAc).

Compound 408

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (s, 1H, *H7*), 7.08 (s, 1H, *H10*), 5.13 (q, *J* = 6.7 Hz, 1H, C*H*CF_3), 4.01 (s, 3H, C9OC*H*$_3$), 3.92 (s, 3H, C8OC*H*$_3$), 3.25 (dq, *J* = 13.7, 7.2 Hz, 1H, C*H*$_a$H$_b$$CH_3$), 3.13 (dq, *J* = 14.4, 7.2 Hz, 1H, CH_a*H*$_b$$CH_3$), 2.39 (s, 3H, ArC*H*$_3$), 1.38 (t, *J* = 7.2 Hz, 1H, CH_2C*H*$_3$), and 0.41 [s, 9H, Si(C*H*$_3$)$_3$].

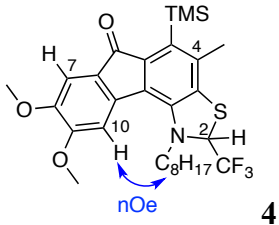
^{13}C NMR (125 MHz, $CDCl_3$): δ 193.3, 154.1, 149.3, 142.3, 141.0, 140.2, 138.1, 136.6, 135.9, 129.7, 127.1, 123.5 (q, *J* = 280 Hz), 107.0, 105.5, 70.1 (q, *J* = 34 Hz), 56.3, 56.2, 49.4, 24.4, 13.6, and 2.8.

IR (neat): 3008, 2979, 2948, 2901, 2838, 1701, 1588, 1547, 1492, 1469, 1386, 1341, 1317, 1249, 1211, 1171, 1128, 1089, 1018, and 961 cm^{-1}.

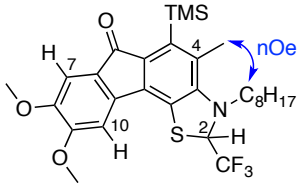
HRMS (ESI-TOF): Calculated for $C_{23}H_{27}F_3NO_3SSi^+$ $[M+H^+]$ 482.1433, found 482.1428.

TLC: R_f 0.1 (11:1 hexanes:EtOAc).

8,9-Dimethoxy-4-methyl-1-octyl-2-(trifluoromethyl)-5-(trimethylsilyl)-1,2-dihydro-6*H*-fluoreno[4,3-*d*]thiazol-6-one (412) and
8,9-Dimethoxy-4-methyl-3-octyl-2-(trifluoromethyl)-5-(trimethylsilyl)-2,3-dihydro-6*H*-fluoreno[3,4-*d*]thiazol-6-one (413)



412



413

Prepared following General Experimental Procedure B. In order of elution (hexanes:EtOAc 11:1), the fluorenone derivatives **412** (43.7 mg) and **413** (19.6 mg) were isolated in 52% and 24% yield and each as an amorphous orange solid, respectively. When this reaction was scaled to the level of 1 mmol, the isolated yields, following MPLC were 59% of **412** and 17% of **413**.

Compound 412

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (s, 1H, *H7*), 7.09 (s, 1H, *H10*), 5.15 (q, *J* = 6.5 Hz, 1H, C*H*CF_3), 4.00 (s, 3H, C9OC*H*$_3$), 3.92 (s, 3H, C8OC*H*$_3$), 3.17 (ddd, *J* = 13.4, 11.6, 5.1 Hz, 1H, NC*H*$_a$H$_b$$CH_2$), 3.01 (ddd, *J* = 13.4, 12.0, 5.1 Hz, 1H, NCH$_a$*H*$_b$$CH_2$), 2.39 (s, 3H, ArC*H*$_3$), 1.93–1.81 (m, 1H, NCH_2C*H*$_a$H$_b$), 1.81–1.70 (m, 1H, NCH_2CH_a*H*$_b$), 1.35–1.20 [m, 10H, (CH_2)$_5$C*H*$_3$], 0.86 (t, *J* = 6.8 Hz, 3H, CH_2C*H*$_3$), and 0.41 [s, 9H, Si(C*H*$_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.3, 154.0, 149.3, 142.6, 140.9, 140.2, 138.0, 136.7, 135.9, 129.6, 127.1, 123.5 (q, *J* = 280 Hz), 107.0, 105.5, 70.4 (q, *J* = 34 Hz), 56.21, 56.20, 55.3, 31.7, 29.5, 29.2, 28.8, 26.9, 24.7, 22.6, 14.0, and 2.8.

IR (neat): 2985, 2958, 2930, 2870, 2856, 1702, 1602, 1589, 1547, 1492, 1469, 1422, 1378, 1340, 1210, 1171, 1129, 1119, 1091, 1016, and 924 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{29}H_{39}F_3NO_3SSi^+$ [M+H$^+$] 566.2372, found 566.2368.

TLC: R_f 0.3 (11:1 hexanes:EtOAc).

Compound 413

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16 (s, 1H, *H7*), 6.90 (s, 1H, *H10*), 5.20 (q, *J* = 6.4 Hz, 1H, C*H*CF_3), 4.03 (s, 3H, C9OC*H*$_3$), 3.91 (s, 3H, C8OC*H*$_3$), 3.19 (ddd, *J* = 14.3, 9.9, 4.7 Hz, 1H, NC*H*$_a$H$_b$$CH_2$), 2.92 (ddd, *J* = 13.9, 10.2, 6.5 Hz, 1H, NCH$_a$*H*$_b$$CH_2$), 2.39 (s, 3H,

ArC*H*$_3$), 1.83–1.73 (m, 1H, NCH$_2$C*H*$_a$H$_b$), 1.67–1.56 (m, 1H, NCH$_2$CH$_a$*H*$_b$), 1.36–1.22 [m, 10H, (C*H*$_2$)$_5$CH$_3$], 0.88 (t, *J* = 7.2 Hz, 3H, CH$_2$C*H*$_3$), and 0.41 [s, 9H, Si(C*H*$_3$)$_3$].

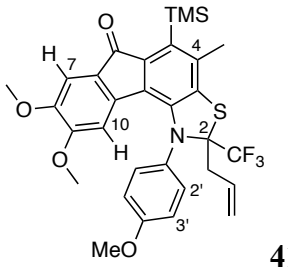
^{13}C NMR (125 MHz, $CDCl_3$): δ 192.7, 154.3, 153.4, 149.3, 141.1, 137.9, 137.4, 135.7, 130.7, 127.1, 125.0, 106.9, 104.6, 71.8 (q, *J* = 34 Hz), 56.4, 56.2, 55.5, 31.8, 29.4, 29.2, 28.5, 26.7, 22.6, 21.3, 14.1, and 2.7. (resonance for CF_3 not observed)

IR (neat): 2956, 2929, 2856, 1702, 1595, 1583, 1547, 1494, 1464, 1443, 1399, 1373, 1361, 1313, 1218, 1194, 1171, 1120, 1098, 1021, and 979 cm^{-1}.

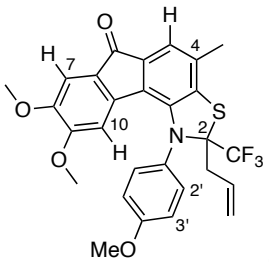
HRMS (ESI-TOF): Calculated for $C_{29}H_{39}F_3NO_3SSi^+$ [M+H$^+$] 566.2372, found 566.2366.

TLC: R_f 0.2 (11:1 hexanes:EtOAc).

2-Allyl-8,9-dimethoxy-1-(4-methoxyphenyl)-4-methyl-2-(trifluoromethyl)-5-(trimethylsilyl)-1,2-dihydro-6*H*-fluoreno[4,3-*d*]thiazol-6-one (415) and 2-Allyl-8,9-dimethoxy-1-(4-methoxyphenyl)-4-methyl-2-(trifluoromethyl)-1,2-dihydro-6*H*-fluoreno[4,3-*d*]thiazol-6-one (415')



415



415'

Prepared following General Experimental Procedure B. The fluorenone derivative **415** (46.8 mg, 77% yield) as isolated as an amorphous orange solid following purification by MPLC (hexanes:EtOAc 3:1). When this reaction was performed in 1,2-dichloroethane, **415** (41%) was accompanied by the (slower eluting) desilylated analog **415'** (22%), also as an amorphous orange solid.

Compound 415

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (dd, *J* = 8.7, 2.8 Hz, 1H, *H2'*), 7.05 (s, 1H, *H7*), 6.96 (dd, *J* = 8.8, 3.0 Hz, 1H, *H6'*), 6.90 (dd, *J* = 8.8, 2.8 Hz, 1H, *H3'* or H5'), 6.68 (dd, *J* = 8.9, 3.0 Hz, 1H, *H5'* or H3'), 6.17 (s, 1H, *H10*), 5.61 (dddd, *J* = 16.9, 10.3, 6.9, 6.9 Hz, 1H, CH_2=C*H*CH_2), 4.99 (dddd, *J* = 10.3, 1.0, 1.0, 1.0 Hz, 1H, C$H_a$$H_b$=$CHCH_2$), 4.93 (dddd, *J* = 16.9, 1.1, 1.1, 1.1 Hz, 1H, $CH_a$$H_b$=$CHCH_2$), 3.83 (s, 3H, C8OC$H_3$), 3.75 (s, 3H, *p*-C$H_3$OPh), 3.62 (s, 3H, C9OC$H_3$), 2.89 (dddd, *J* = 15.1, 6.5, 1.2, 1.2 Hz, 1H, CH_2=CHC$H_a$$H_b$), 2.68 (br dd, *J* = 15.2, 7.5 Hz, 1H, CH_2=$CHCH_a$$H_b$), 2.41 (s, 3H, ArC$H_3$), and 0.42 [s, 9H, Si(C$H_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.5, 157.8, 153.4, 148.5, 140.9, 140.7, 138.7, 136.7, 136.3, 136.0, 135.5, 130.5, 127.9 (likely 2 carbons), 127.1, 126.7, 125.3 (q, *J* = 285 Hz), 120.0, 114.68, 114.64, 107.3, 106.2, 81.5 (q, *J* = 29 Hz), 56.4, 56.0, 55.5, 36.2, 23.8, and 3.0.

IR (neat): 3007, 2951, 2902, 2838, 1700, 1640, 1604, 1547, 1508, 1491, 1464, 1442, 1392, 1379, 1298, 1249, 1188, 1162, 1133, 1086, 1032, and 976 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{31}H_{33}F_3NO_4SSi^+$ [M+H$^+$] 600.1852, found 600.1843.

TLC: R_f 0.3 (3:1 hexanes:EtOAc).

Compound 415'

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (dd, *J* = 8.7, 2.8 Hz, 1H, *H2'*), 7.13 (s, 1H, *H7* or H5), 7.10 (s, 1H, H7 or *H5*), 6.98 (dd, *J* = 8.8, 3.0 Hz, 1H, *H6'*), 6.92 (dd, *J* = 8.8, 2.7 Hz, 1H, *H3'* or H5'), 6.69 (dd, *J* = 8.9, 3.0 Hz, 1H, *H5'* or H3'), 6.08 (s, 1H, *H10*), 5.62 (dddd, *J* = 16.9, 10.3, 7.0, 7.0 Hz, 1H, CH_aH_b=C*H*CH_2), 5.01 (dddd, *J* = 10.3, 1.0, 1.0, 1.0 Hz, 1H, CH_a*H*$_b$=$CHCH_2$), 4.95 (dddd, *J* = 16.9, 1.1, 1.1, 1.1 Hz, 1H, C*H*$_a$$H_b$=$CHCH_2$), 3.84 (s, 3H, C8OC*H*$_3$), 3.76 (s, 3H, *p*-C*H*$_3$OPh), 3.60 (s, 3H, C9OC*H*$_3$), 2.90 (dddd, *J* = 15.0, 6.3, 1.2, 1.2 Hz, 1H, CH_2=CHC*H*$_a$$H_b$), 2.68 (br dd, *J* = 15.0, 7.4 Hz, 1H, CH_2=$CHCH_a$*H*$_b$), and 2.30 (s, 3H, ArC*H*$_3$).

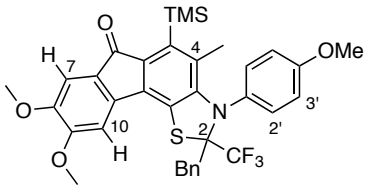
^{13}C NMR (125 MHz, $CDCl_3$): δ 192.4, 157.9, 153.6, 148.5, 140.7, 138.3, 137.5, 136.0, 134.7, 130.4, 130.1, 128.2, 127.4, 127.1, 126.6, 120.8, 120.1, 114.9, 114.7, 107.7, 106.6, 56.4, 56.1, 55.5, 36.4, and 20.8. (*C*F_3 and *C*CF_3 carbons not observed.)

IR (neat): 3004, 2940, 2838, 1699, 1600, 1586, 1508, 1492, 1464, 1442, 1377, 1217, 1190, 1166, 1131, 1072, 1032, and 986 cm^{-1}.

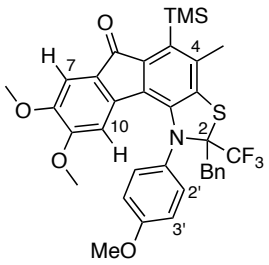
HRMS (ESI-TOF): Calculated for $C_{28}H_{25}F_3NO_4S^+$ [M+H$^+$] 528.1456, found 528.1450.

TLC: R_f 0.1 (3:1 hexanes:EtOAc).

2-Benzyl-8,9-dimethoxy-3-(4-methoxyphenyl)-4-methyl-2-(trifluoromethyl)-5-(trimethylsilyl)-2,3-dihydro-6*H*-fluoreno[3,4-*d*]thiazol-6-one (417') and 2-Benzyl-8,9-dimethoxy-1-(4-methoxyphenyl)-4-methyl-2-(trifluoromethyl)-5-(trimethylsilyl)-1,2-dihydro-6*H*-fluoreno[4,3-*d*]thiazol-6-one (417)



417'



417

Prepared following General Experimental Procedure B. In order of elution (hexanes:EtOAc 5:1), the fluorenone derivatives **417'** (4.0 mg) and **417** (48.6 mg) were isolated in 7% and 81% yield and each as an amorphous orange solid.

Compound 417'

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (dd, *J* = 8.8, 2.7 Hz, 1H, *H2'*), 7.28-7.25 (m, 3H, $C_6H_5CH_2N$), 7.22-7.19 (m, 2H, $C_6H_5CH_2N$), 7.16 (s, 1H, *H7*), 6.99 (dd, *J* = 8.8, 3.0 Hz, 1H, *H6'*), 6.873 (dd, *J* = 8.6, 2.7 Hz, 1H, *H3'*), 6.870 (s, 1H, *H10*), 6.81 (dd, *J* = 8.8, 3.0 Hz, 1H, *H5'*), 3.99 (s, 3H, C8OC*H*$_3$), 3.91 (s, 3H, *p*-C*H*$_3$OPh), 3.84 (s, 3H, C9OC*H*$_3$), 3.39 (d, *J* = 14.3 Hz, 1H, PhC*H*$_a$H$_b$), 2.99 (d, *J* = 14.4 Hz, 1H, PhCH$_a$*H*$_b$), 1.80 (s, 3H, ArC*H*$_3$), and 0.32 [s, 9H, Si(C*H*$_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 192.4, 158.2, 154.1, 152.8, 149.2, 141.6, 137.3, 135.9, 135.2, 134.2, 131.0, 130.6, 129.6, 129.3, 128.1, 127.6, 127.5, 114.7, 114.5, 106.9, 105.1, 56.5, 56.2, 55.5, 39.7, 21.6, and 2.6 (signal-to-noise was insufficient to allow detection of the quartets expected for CF_3 and C2 and two additional aromatic carbons).

IR (neat): 3007, 2952, 2902, 2836, 1700, 1592, 1545, 1508, 1493, 1457, 1358, 1315, 1248, 1216, 1181, 1113, 1094, 1021, and 973 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{35}H_{35}F_3NO_4SSi^+$ [M+H$^+$] 650.2008, found 650.2006.

TLC: R_f 0.3 (5:1 hexanes:EtOAc).

Compound 417

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (dd, *J* = 8.8, 2.8 Hz, 1H, *H2'*), 7.26-7.23 (m, 3H, $C_6H_5CH_2N$), 7.18-7.14 (m, 2H, $C_6H_5CH_2N$), 7.05 (s, 1H, *H7*), 7.01 (dd, *J* = 8.7, 3.0 Hz, 1H, *H6'*), 6.91 (dd, *J* = 8.9, 2.7 Hz, 1H, *H3'*), 6.71 (dd, *J* = 8.9, 3.0 Hz, 1H, *H5'*), 6.27 (s,

1H, *H10*), 3.83 (s, 3H, C8OCH_3), 3.76 (s, 3H, *p*-CH_3OPh), 3.68 (s, 3H, C9OCH_3), 3.51 (d, J = 14.2 Hz, 1H, PhCH_aH$_b$), 2.95 (d, J = 14.3 Hz, 1H, PhCH$_a$$H_b$), 2.38 (s, 3H, ArC$H_3$), and 0.42 [s, 9H, Si(C$H_3$)$_3$].

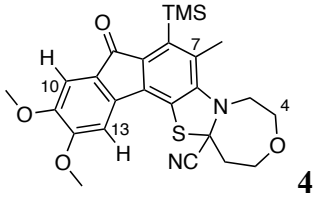
^{13}C NMR (125 MHz, $CDCl_3$): δ 193.5, 158.0, 153.4, 148.6, 141.4, 140.7, 138.8, 136.7, 136.3, 136.0, 135.4, 134.1, 130.8, 128.9, 128.01, 127.98 (likely 2 carbons), 127.6, 126.7, 125.4 (q, J = 285 Hz), 114.9, 114.8, 107.3, 106.2, 82.3 (q, J = 28 Hz), 56.5, 56.0, 55.5, 39.4, 23.8, and 3.0.

IR (neat): 3008, 2963, 2949, 2902, 2838, 1700, 1604, 1589, 1548, 1508, 1491, 1456, 1358, 1315, 1249, 1212, 1180, 1132, 1116, 1081, 1032, 1017, and 977 cm^{-1}.

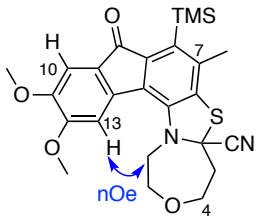
HRMS (ESI-TOF): Calculated for $C_{35}H_{35}F_3NO_4SSi^+$ [M+H$^+$] 650.2008, found 650.2001.

TLC: R_f 0.1 (5:1 hexanes:EtOAc).

11,12-Dimethoxy-7-methyl-9-oxo-8-(trimethylsilyl)-1,2,4,5-tetrahydro-5a*H*,9*H*-fluoreno[4',3':4,5]thiazolo[3,2-*d*][1,4]oxazepine-5a-carbonitrile (419') and 11,12-Dimethoxy-7-methyl-9-oxo-8-(trimethylsilyl)-1,2,4,5-tetrahydro-9*H*,14a*H*-fluoreno[3',4':4,5]thiazolo[3,2-*d*][1,4]oxazepine-14a-carbonitrile (419)



419'



419

Prepared following General Experimental Procedure B. In order of elution (hexanes:EtOAc 3:1), the fluorenone derivatives **419'** (4.6 mg) and **419** (23.6 mg) were isolated in 16% and 82% yield and each as an amorphous orange solid.

Compound 419'

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (s, 1H, *H10*), 6.82 (s, 1H, *H13*), 4.24 (dd, *J* = 13.0, 6.3 Hz, 1H, OC4H_aH$_b$CH$_2$), 4.06 (dd, *J* = 13.4, 4.5 Hz, 1H, OC2H_aH$_b$CH$_2$), 4.02 (dd, *J* = 13.2, 8.9 Hz, 1H, OC4H$_a$$H_bCH_2$), 4.02 (s, 3H, C12OC$H_3$), 3.92 (s, 3H, C11OC$H_3$), 3.91 (dd, *J* = 12.5, 9.7 Hz, 1H, OC2H$_a$$H_bCH_2$), 3.75 (dd, *J* = 15.7, 9.3 Hz, 1H, NC1H_aH$_b$CH$_2$), 2.98 (ddd, *J* = 15.8, 9.0, 0.8 Hz, 1H, C5H_aH$_b$CH$_2$), 2.88 (dd, *J* = 15.8, 4.6 Hz, 1H, NC1H$_a$$H_bCH_2$), 2.83 (dd, *J* = 15.8, 6.5 Hz, 1H, C5H$_a$$H_bCH_2$), 2.39 (s, 3H, ArC$H_3$), and 0.42 [s, 9H, Si(C$H_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 192.8, 154.5, 153.4, 149.6, 141.7, 139.1, 137.3, 136.4, 132.4, 127.0, 120.5, 107.0, 104.6, 75.8, 71.5, 66.4, 56.3, 56.2, 53.0, 39.0, 21.5, and 2.7. (one sp^2- or cyano-carbon not observed.)

IR (neat): 3008, 2985, 2949, 2856, 1705, 1596, 1547, 1494, 1442, 1421, 1370, 1355, 1315, 1192, 1130, 1099, 1018, and 854 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{25}H_{29}N_2O_4SSi^+$ [M+H$^+$] 481.1617, found 481.1616.

TLC: R_f 0.15 (3:1 hexanes:EtOAc).

Compound 419

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (s, 1H, *H10*), 6.94 (s, 1H, *H13*), 4.26 (dd, *J* = 13.2, 6.5 Hz, 1H, OC4H_aH$_b$CH$_2$), 4.15 (dd, *J* = 12.4, 4.8 Hz, 1H, OC2H_aH$_b$CH$_2$), 4.02 (dd, *J* = 13, 9 Hz, 1H, OC4H$_a$$H_bCH_2$), 4.02 (s, 3H, C12OC$H_3$), 4.00 (dd, *J* = 12.2, 9.7 Hz, 1H, OC2H$_a$$H_bCH_2$), 3.92 (s, 3H, C11OC$H_3$), 3.77 (dd, *J* = 15.7, 9.1 Hz, 1H, NC1H_aH$_b$CH$_2$),

3.07 (ddd, J = 15.7, 4.8 Hz, 1H, NC1H$_a$*H$_b$*CH$_2$), 2.94 (ddd, J = 16.0, 8.8, 1.0 Hz, 1H, C5*H$_a$*H$_b$CH$_2$), 2.86 (ddd, J = 16.0, 6.7, 1.0 Hz, 1H, C5H$_a$*H$_b$*CH$_2$), 2.37 (s, 3H, ArC*H$_3$*), and 0.42 [s, 9H, Si(C*H$_3$*)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.0, 154.0, 149.5, 142.1, 140.8, 140.6, 139.6, 136.7, 135.9, 130.5, 127.2, 120.7, 107.2, 105.7, 74.3, 72.0, 66.7, 56.5, 56.3, 53.6, 39.2, 24.8, and 2.7.

IR (neat): 3007, 2985, 2950, 2858, 1703, 1587, 1545, 1492, 1456, 1422, 1362, 1347, 1317, 1212, 1193, 1147, 1125, 1093, 1043, 1014, and 985 cm^{-1}.

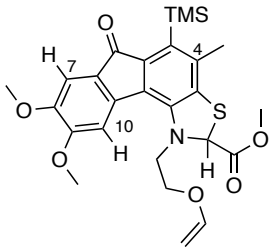
HRMS (ESI-TOF): Calculated for $C_{25}H_{29}N_2O_4SSi^+$ [M+H$^+$] 481.1617, found 481.1613.

TLC: R_f 0.1 (3:1 hexanes:EtOAc).

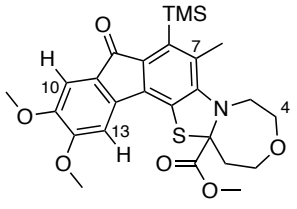
Methyl 8,9-dimethoxy-4-methyl-6-oxo-5-(trimethylsilyl)-1-(2-(vinyloxy)ethyl)-1,6-dihydro-2*H*-fluoreno[4,3-*d*]thiazole-2-carboxylate (423),

Methyl 11,12-dimethoxy-7-methyl-9-oxo-8-(trimethylsilyl)-1,2,4,5-tetrahydro-5a*H*,9*H*-fluoreno[4',3':4,5]thiazolo[3,2-*d*][1,4]oxazepine-5a-carboxylate (421-regio) and

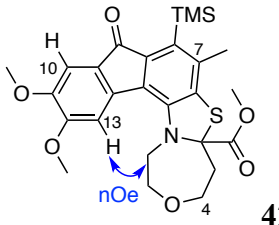
Methyl 11,12-dimethoxy-7-methyl-9-oxo-8-(trimethylsilyl)-1,2,4,5-tetrahydro-9*H*,14a*H*-fluoreno[3',4':4,5]thiazolo[3,2-*d*][1,4]oxazepine-14a-carboxylate (421)



423



421-regio



421

Prepared following General Experimental Procedure B. In order of elution (hexanes:EtOAc 2:1), the fluorenone derivatives **423** (3.0 mg), **421-regio** (8.3 mg), and **421** (26.5 mg) were isolated in 6%, 17% and 53% yield and each as a foamy amorphous orange solid.

Compound 423

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (s, 1H, *H10*), 7.17 (s, 1H, *H7*), 6.49 (dd, *J* = 14.3, 6.8 Hz, 1H, OC*H*=CH_2), 5.59 (s, 1H, NC*H*S), 4.21 (dd, *J* = 14.4, 2.5 Hz, 1H, OCH=C$H_a$$H_b$), 4.10 (dd, *J* = 6.8, 2.5 Hz, 1H, OCH=$CH_a$$H_b$), 4.02–4.00 (m, 2H, NCH_2CH_2O), 4.01 (s, 3H, C9OCH_3), 3.91 (s, 3H, C8OCH_3), 3.74 (s, 3H, COOCH_3), 3.51 (ddd, *J* = 14.8, 5.0, 5.0 Hz, 1H, NC$H_a$$H_b$$CH_2$), 3.30 (ddd, *J* = 14.8, 5.3, 5.3 Hz, 1H, $NCH_aH_bCH_2$), 2.36 (s, 3H, ArCH_3), and 0.40 [s, 9H, Si(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.5, 169.7, 154.0, 151.0, 149.2, 143.3, 142.2, 140.2, 138.2, 136.8, 136.1, 129.8, 127.3, 106.9, 106.1, 87.6, 69.7, 66.6, 56.5, 56.2, 52.9, 52.4, 24.7, and 2.8.

IR (neat): 3006, 2986, 2955, 1750, 1700, 1589, 1545, 1493, 1456, 1439, 1421, 1387, 1363, 1313, 1211, 1194, 1126, 1099, 1073, 1020, and 895 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{26}H_{32}NO_6SSi^+$ [M+H$^+$] 514.1720, found 514.1715.

TLC: R_f 0.4 (2:1 hexanes:EtOAc).

Compound 421-regio

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (s, 1H, *H10*), 6.82 (s, 1H, *H13*), 4.16 (dd, *J* = 13.0, 7.1 Hz, 1H, OC4H_aH$_b$CH$_2$), 4.00 (s, 3H, C12OCH_3), 3.97 (dd, *J* = 12.3, 5.5 Hz, 1H, OC2H_aH$_b$CH$_2$), 3.90 (s, 3H, C11OCH_3), 3.84 (dd, *J* = 12.3, 8.6 Hz, 1H, OC2H$_a$$H_bCH_2$), 3.77 (dd, *J* = 15.6, 8.6 Hz, 1H, NC1H_aH$_b$CH$_2$), 3.73 (s, 3H, COOCH_3), 3.65 (dd, *J* = 12.9, 8.8 Hz, 1H, OC4H$_a$$H_bCH_2$), 3.11 (dd, *J* = 15.6, 5.5 Hz, 1H, NC1H$_a$$H_bCH_2$), 2.99 (dd, *J* = 15.9, 7.1 Hz, 1H, C5H_aH$_b$CH$_2$), 2.82 (dd, *J* = 15.8, 8.9 Hz, 1H, C5H$_a$$H_bCH_2$), 2.40 (s, 3H, ArC$H_3$), and 0.40 [s, 9H, Si(C$H_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 192.8, 171.9, 154.2, 149.1, 141.1, 137.7, 137.4, 135.3, 135.0, 129.9, 128.0, 127.2, 106.8, 104.7, 84.7, 71.5, 66.9, 56.3, 56.2, 53.6, 53.5, 37.0, 21.8, and 2.7.

IR (neat): 2953, 2901, 2856, 2839, 1740, 1699, 1595, 1582, 1494, 1463, 1442, 1372, 1358, 1316, 1218, 1194, 1128, 1099, 1068, 1020, and 974 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{26}H_{32}NO_6SSi^+$ [M+H$^+$] 514.1720, found 514.1716.

TLC: R_f 0.25 (2:1 hexanes:EtOAc).

Compound 421

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (s, 1H, *H10*), 7.01 (s, 1H, *H13*), 4.18 (dd, *J* = 13.0, 7.1 Hz, 1H, OC4H_aH$_b$CH$_2$), 4.06 (dd, *J* = 12.3, 5.5 Hz, 1H, OC2H_aH$_b$CH$_2$), 4.00 (s, 3H, C12OCH_3), 3.91 (dd, *J* = 12.3, 8.6 Hz, 1H, OC2H$_a$$H_bCH_2$), 3.91 (s, 3H, C11OC$H_3$), 3.78 (dd, *J* = 15.6, 8.6 Hz, 1H, NC1H_aH$_b$CH$_2$), 3.74 (s, 3H, COOCH_3), 3.64 (dd, *J* = 12.9, 8.8 Hz, 1H, OC4H$_a$$H_bCH_2$), 3.28 (dd, *J* = 15.6, 5.5 Hz, 1H, NC1H$_a$$H_bCH_2$), 3.00 (dd, *J* = 15.9, 7.1 Hz, 1H, C5H_aH$_b$CH$_2$), 2.79 (dd, *J* = 15.8, 8.9 Hz, 1H, C5H$_a$$H_bCH_2$), 2.31 (s, 3H, ArC$H_3$), and 0.39 [s, 9H, Si(C$H_3$)$_3$].

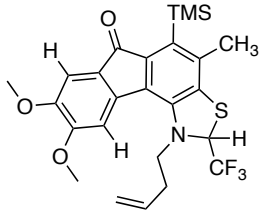
^{13}C NMR (125 MHz, $CDCl_3$): δ 193.3, 172.0, 153.9, 149.0, 144.5, 141.6, 140.2, 137.5, 136.7, 135.4, 128.6, 127.2, 107.1, 105.7, 83.5, 72.0, 67.3, 56.4, 56.2, 54.4, 53.5, 37.0, 24.4, and 2.8.

IR (neat): 3005, 2953, 2901, 2854, 2838, 1741, 1700, 1588, 1543, 1491, 1463, 1442, 1352, 1318, 1282, 1210, 1194, 1149, 1126, 1093, 1067, 1015, and 974 cm^{-1}.

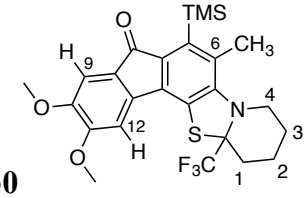
HRMS (ESI-TOF): Calculated for $C_{26}H_{32}NO_6SSi^+$ [M+H$^+$] 514.1720, found 514.1719.

TLC: R_f 0.1 (2:1 hexanes:EtOAc).

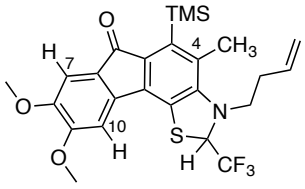
1-(But-3-en-1-yl)-8,9-dimethoxy-4-methyl-2-(trifluoromethyl)-5-(trimethylsilyl)-1,2-dihydro-6*H*-fluoreno[4,3-*d*]thiazol-6-one (430), 10,11-Dimethoxy-6-methyl-13a-(trifluoromethyl)-7-(trimethylsilyl)-1,3,4,13a-tetrahydro-2*H*,8*H*-fluoreno[3',4':4,5]thiazolo[3,2-*a*]pyridin-8-one (429-regio), 3-(But-3-en-1-yl)-8,9-dimethoxy-4-methyl-2-(trifluoromethyl)-5-(trimethylsilyl)-2,3-dihydro-6*H*-fluoreno[3,4-*d*]thiazol-6-one (430-regio), 10,11-Dimethoxy-6-methyl-4-(trifluoromethyl)-7-(trimethylsilyl)-2,3,3a,4-tetrahydro-1*H*,8*H*-fluoreno[3,4-*b*]pyrrolo[1,2-*d*][1,4]thiazin-8-one (431) and 10,11-Dimethoxy-6-methyl-13a-(trifluoromethyl)-7-(trimethylsilyl)-1,3,4,13a-tetrahydro-2*H*,8*H*-fluoreno[3',4':4,5]thiazolo[3,2-*a*]pyridin-8-one (429)



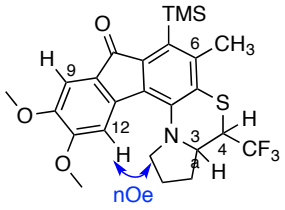
430



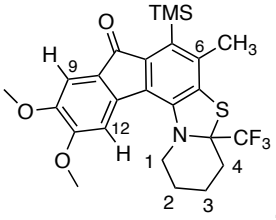
429-regio



430-regio



431



429

Prepared following General Procedure B. In order of elution (hexanes:EtOAc 11:1), the fluorenone derivatives **430** (13.0 mg), **429-regio** (6.8 mg)/**430-regio** (2.3 mg), **431** (5.6 mg), and **429** (16.0 mg) were isolated in 28%, 14%/5%, 12%, and 34% yield, each as a foamy amorphous orange solid. The **429-regio** and **430-regio** isomers coeluted and were characterized as a mixture.

Compound 430

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (s, 1H, *H7*), 7.07 (s, 1H, *H10*), 5.76 (dddd, *J* = 17.0, 10.2, 6.6, 6.5 Hz, 1H, CH_2=C*H*CH_2), 5.18 (q, *J* = 6.7 Hz, 1H, C*H*CF_3), 5.12 (dddd, *J* = 17.0, 1.5, 1.5, 1.5 Hz, 1H, =$CH_{cis}H_{trans}$), 5.08 (dddd, *J* = 10.2, 1.3, 1.3, 1.3 Hz, 1H, =C$H_{cis}H_{trans}$), 4.00 (s, 3H, C9OCH_3), 3.92 (s, 3H, C8OCH_3), 3.28 (ddd, *J* = 13.6, 10.5, 5.5 Hz, 1H, NCH_bH_a), 3.13 (ddd, *J* = 13.7, 11.1, 5.5 Hz, 1H, NCH_aH_b), 2.67–2.57 (m, 1H, CH_2=CHC$H_a$$H_b$), 2.53–2.44 (m, 1H, CH_2=CHC$H_a$$H_b$), 2.39 (s, 3H, ArC$H_3$), and 0.41 [s, 9H, $(CH_3)_3$Si].

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.2, 154.1, 149.3, 142.1, 141.0, 140.3, 138.2, 136.5, 136.0, 133.5, 129.7, 127.2, 117.7, 107.0, 105.5, 70.4 (q, J = 34 Hz), 56.3, 56.2, 54.1, 32.6, 24.4, and 2.8. (CF_3 carbon not observed)

IR (neat): 2985, 2951, 2942, 2838, 1702, 1602, 1588, 1547, 1464, 1367, 1339, 1209, 1129, 1090, 1059, and 923 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{25}H_{29}F_3NO_3SSi^+$ [M+H^+] 508.1584, found 508.1574.

TLC: R_f 0.25 (11:1 hexanes:EtOAc).

All of the characterization data for **429-regio** and **430-regio** were obtained from a sample containing both of these coeluting compounds.

Compound 429-regio

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16 (s, 1H, *H*9), 6.91 (s, 1H, *H*12), 4.03 (s, 3H, C11OC*H*$_3$), 3.91 (s, 3H, C10OC*H*$_3$), 3.36-3.30 (ddd, J = 12.6, 6.6, 3.7 Hz, 1H, NC*H*$_a$H$_b$), 2.74 (ddd, J = 12.7, 8.9, 4.0 Hz, 1H, NCH$_a$*H*$_b$), 2.4 (s, 3H, ArC*H*$_3$), 2.31 (ddd, J = 15.0, 10.6, 5.7 Hz, 1H, NC*H*$_a$H$_b$), 2.27 (ddd, J = 15, 6, 4 Hz, 1H, NCH$_a$*H*$_b$), 1.98-1.84 (m, 2H, C2*H*$_a$H$_b$ and C3*H*$_a$H$_b$), 1.82-1.74 (m, 1H, C2H$_a$*H*$_b$ or C3H$_a$*H*), 1.68 (ddddd, J = 13.5, 8.7, 8.7, 6.7, 3.9 Hz, 1H, C2H$_a$*H*$_b$ or C3H$_a$*H*$_b$), and 0.40 (s, 9H, TMS) (from the mixture of **429-regio** and **430-regio**).

^{13}C NMR (125 MHz, $CDCl_3$): δ 192.9, 154.3, 149.2, 140.6, 137.8, 137.7, 135.7, 134.2, 131.1, 127.1, 106.9, 104.7, 56.3, 56.2, 48.4, 24.8, 21.3, 20.9, 17.3, and 2.8. (One aromatic carbon, the *C*F_3 carbon, and the *C*CF_3 were not observed in the 1D ^{13}C spectrum; the *C*CF_3 resonance was observed as a cross peak at 81.4 ppm in the HMBC spectrum.)

IR (neat): 2962, 2953, 2904, 2839, 1702, 1595, 1583, 1548, 1494, 1421, 1362, 1349, 1312, 1218, 1194, 1129, 1099, 1022, and 908 cm^{-1} (from the mixture of **429-regio** and **430-regio**).

HRMS (ESI-TOF): Calculated for $C_{25}H_{29}F_3NO_3SSi^+$ [M+H^+] 508.1584, found 508.1569.

TLC: R_f 0.20 (11:1 hexanes:EtOAc) (from the mixture of **429-regio** and **430-regio**).

Compound 430-regio

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16 (s, 1H, *H*7), 6.89 (s, 1H, *H*10), 5.83 (dddd, J = 17.1, 10.3, 6.8, 6.8 Hz, 1H, CH_2=C*H*CH_2), 5.23 (q, J = 6.4 Hz, 1H, C*H*CF_3), 5.14 (dddd, J = 17.1, 1.5, 1.5, 1.5 Hz, 1H, =$CH_{cis}H_{trans}$), 5.10 (dddd, J = 10.2, 1.5, 1.5, 1.5 Hz, 1H, =C*H*$_{cis}$H$_{trans}$), 4.03 (s, 3H, C9OC*H*$_3$), 3.91 (s, 3H, C8OC*H*$_3$), 3.30 (ddd, J = 14, 9.2, 5.1

Hz, 1H, NCH_aH$_b$), 3.01 (ddd, J = 14.1, 9.6, 6.7 Hz, 1H, NCH$_a$$H_b$), 2.58-2.49 (dddddd, J = 14.7, 9.2, 6.8, 6.8, 1.3, 1.3 Hz, 1H, m, 1H, CH$_2$=CHCH_aH$_b$), 2.39 (s, 3H, C4CH_3), 2.3 (overlapped m, 1H, CH$_2$=CHCH$_a$$H_b$), and 0.41 [s, 9H, (C$H_3$)$_3$Si] (from the mixture of **429-regio** and **430-regio**).

^{1}H NMR (500 MHz, C_6D_6): δ 7.14 (s, 1H, *H*7), 6.92 (s, 1H, *H*10), 5.57 (dddd, J = 17.1, 10.3, 6.7, 6.7 Hz, 1H, CH$_2$=C*H*CH$_2$), 4.99–4.96 (overlapped m, 1H, =CH$_{cis}$$H_{trans}$), 4.94 (dddd, J = 10.3, 1.5, 1.5, 1.5 Hz, 1H, =CH_{cis}H$_{trans}$), 4.53 (q, J = 6.7 Hz, 1H, CF$_3$C*H*), 3.37 (s, 3H, C9OCH_3), 3.21 (s, 3H, C8OCH_3), 2.74 (ddd, J = 14.5, 9.7, 5.2 Hz, 1H, NCH_aH$_b$), 2.59 (ddd, J = 14.1, 9.6, 6.8 Hz, 1H, NCH$_a$$H_b$), 2.29 (s, 3H, C4C$H_3$), 2.08 (dddddd, J = 14.5, 8.1, 6.6, 6.6, 1.3, 1.3 Hz, 1H, CH$_2$=CHCH_aH$_b$), 1.92–1.83 (overlapped m, 1H, CH$_2$=CHCH$_a$$H_b$), and 0.60 [s, 9H, (C$H_3$)$_3$Si] (from the mixture of **429-regio** and **430-regio**).

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.2, 152.6, 134.3, 124.7, 117.5, 106.9, 104.6, 100.0, 56.4, 54.9, 32.8, 29.7, 21.3, and 2.7. Only the clearly identifiable resonances are reported for the minor component of this sample, which comprised an ca. 3:1 ratio of **429-regio**:**430-regio**.

IR (neat): 2962, 2953, 2904, 2839, 1702, 1595, 1583, 1548, 1494, 1421, 1362, 1349, 1312, 1218, 1194, 1129, 1099, 1022, and 908 cm^{-1} (from the mixture of **429-regio** and **430-regio**).

HRMS (ESI-TOF): Calculated for $C_{25}H_{29}F_3NO_3SSi^+$ [M+H$^+$] 508.1584, found 508.1569.

TLC: R_f 0.20 (11:1 hexanes:EtOAc) (from the mixture of **429-regio** and **430-regio**).

Compound 431

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (s, 1H, *H12*), 7.14 (s, 1H, *H9*), 4.25 (ddd, J = 9.5, 5.7, 4.0 Hz, 1H, *H3a*), 4.02 (qd, J = 8.6, 4.2 Hz, 1H, *H4*), 3.98 (s, 3H, C11OCH_3), 3.91 (s, 3H, C10OCH_3), 3.57 (ddd, J = 9.9, 7.4, 3.6 Hz, 1H, NCH_aH$_b$CH$_2$), 2.91 (ddd, J = 9.4, 9.4, 6.4 Hz, 1H, NCH$_a$$H_bCH_2$), 2.44 (s, 3H, ArC$H_3$), 2.44–2.35 (m, 1H, C2$H_aH_b$), 2.13–2.07 (m, 1H, C2H$_a$$H_b$), 2.06–2.02 (m, 1H, C3$H_aH_b$), 1.98–1.87 (m, 1H, C3H$_a$$H_b$), and 0.40 [s, 9H, Si(C$H_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 194.1, 153.9, 148.8, 142.1, 141.3, 140.1, 138.6, 135.4, 135.3, 135.1, 126.7, 106.7, 106.6, 59.1, 56.15, 56.14, 54.9, 50.6 (q, J = 27 Hz), 27.2, 24.8, 21.7, and 2.8. (CF_3 carbon not observed)

IR (neat): 2986, 2901, 2837, 1701, 1591, 1530, 1464, 1455, 1441, 1361, 1351, 1311, 1245, 1213, 1185, 1126, 1083, 1072, 1055, 1018, and 970 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{25}H_{29}F_3NO_3SSi^+$ [M+H^+] 508.1584, found 508.1588.

TLC: R_f 0.15 (11:1 hexanes:EtOAc).

Compound 429

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.15 (s, 1H, *H*12), 7.12 (s, 1H, *H*9), 3.98 (s, 3H, C11OC*H*$_3$), 3.91 (s, 3H, C10OC*H*$_3$), 3.42 (ddd, *J* = 12.2, 6.9, 3.7 Hz, 1H, NC*H*$_a$H$_b$), 2.87 (ddd, *J* =12.2, 8.9, 3.7 Hz, 1H, NCH$_a$*H*$_b$), 2.38 (s, 3H, C6C*H*$_3$), 2.32 (ddd, *J* = 14.9, 10.6, 6.0 Hz, 1H, C4*H*$_a$H$_b$), 2.27 (ddd, *J* = 14.9, 5.2, 3.8 Hz, 1H, C4H$_a$*H*$_b$), 1.97–1.88 (m, 2H, C2*H*$_a$H$_b$ and C3*H*$_a$H$_b$), 1.81 (*J* = 13.0, 6.3, 6.3, 6.3, 3.8 Hz, 1H, C2H$_a$*H*$_b$ or C3H$_a$*H*$_b$), 1.67 (ddddd, *J* = 13.7, 8.8, 7.5, 7.5, 3.9 Hz, 1H, C2H$_a$*H*$_b$ or C3H$_a$*H*$_b$), and 0.40 (s, 9H, TMS).

^{1}H NMR (500 MHz, C_6D_6): δ 7.19 (s, 1H, *H9*), 7.07 (s, 1H, *H12*), 3.43 (s, 3H, C11OC*H*$_3$), 3.26 (s, 3H, C10OC*H*$_3$), 2.99 (ddd, *J* = 3.7, 7.1, 12.2 Hz, 1H, NC*H*$_a$H$_b$), 2.52 (ddd, *J* = 3.7, 8.6, 12.5 Hz, 1H, NCH$_a$*H*$_b$), 2.31 (s, 3H, ArC*H*$_3$), 1.93 (ddd, *J* = 15.1, 11.5, 5.5 Hz, 1H, C4*H*$_a$H$_b$), 1.87 (ddd, *J* = 15.1, 5.6, 3.7 Hz, 1H, C4H$_a$*H*$_b$), 1.56–1.46 (m, 1H, C2H$_a$*H*$_b$ or C3H$_a$*H*$_b$), 1.35-1.27 (m, 1H, C2*H*$_a$H$_b$ or C3*H*$_a$H$_b$), 1.28-1.20 (m, 1H, C2*H*$_a$H$_b$ or C3*H*$_a$H$_b$), 1.08 (ddddd, *J* = 13.6, 8.6, 8.0, 7.2, 3.9 Hz, 1H, C2H$_a$*H*$_b$ or C3H$_a$*H*$_b$), and 0.57 (s, 9H, TMS).

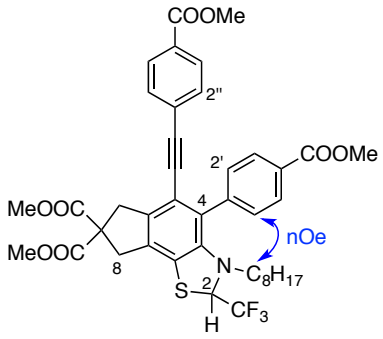
^{13}C NMR (125 MHz, $CDCl_3$): δ 193.4, 154.1, 149.2, 144.7, 142.6, 139.8, 137.9, 136.8, 136.0, 129.6, 127.2, 125.2 (q, *J* = 283 Hz), 106.9, 105.6, 80.8 (q, *J* = 28 Hz), 56.22, 56.17, 49.0, 24.5, 24.0, 20.9, 17.0, and 2.8.

IR (neat): 2986, 2952, 2839, 1701, 1590, 1492, 1440, 1421, 1339, 1316, 1213, 1192, 1162, 1140, 1086, 1030, 1013, and 895 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{25}H_{29}F_3NO_3SSi^+$ [M+H^+] 508.1584, found 508.1585.

TLC: R_f 0.10 (11:1 hexanes:EtOAc).

Dimethyl 4-(4-(methoxycarbonyl)phenyl)-5-((4-(methoxycarbonyl)phenyl)ethynyl)-1-octyl-2-(trifluoromethyl)-1,2,6,8-tetrahydro-7*H*-indeno[4,5-*d*]thiazole-7,7-dicarboxylate (426)



Prepared following General Experimental Procedure B. The dihydrobenzothiazole derivative **426** (15.6 mg) was isolated in 47% yield and as a light yellow, foamy amorphous solid, following purification by MPLC (hexanes:EtOAc 6:1).

Compound 426

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (nfod, *J* = 8.7 Hz, 2H, *H3' or H3''*), 7.93 (nfod, *J* = 8.7 Hz, 2H, *H3'' or H3'*), 7.61 (nfod, *J* = 8.9 Hz, 2H, *H2''*), 7.26 (nfod, *J* = 8.9 Hz, 2H, *H2'*), 5.09 (q, *J* = 6.3 Hz, 1H, NC*H*S), 3.96 (s, 3H, ArCOOC*H*$_3$), 3.91 (s, 3H, ArCOOC*H*$_3$), 3.812 (s, 3H, CCOOC*H*$_3$), 3.806 (s, 3H, CCOOC*H*$_3$), 3.78 (overlapped, 1H, ArC6*Ha*Hb), 3.75 (d, *J* = 17.4 Hz, 1H, ArC6Ha*Hb*), 3.61 (d, *J* = 17.0 Hz, 1H, ArC8*Ha*Hb), 3.55 (d, *J* = 17.0 Hz, 1H, ArC8Ha*Hb*), 2.69 (ddd, *J* = 14.3, 8.8, 5.7 Hz, 1H, NC*H*$_a$H$_b$), 2.43 (ddd, *J* = 14.1, 9.4, 7.3 Hz, 1H, NCH$_a$*H*$_b$), 1.26-0.66 [m, 12H, (C*H*$_2$)$_6$CH$_3$], and 0.86 (t, *J* = 7.3 Hz, 3H, (CH$_2$)$_6$C*H*$_3$).

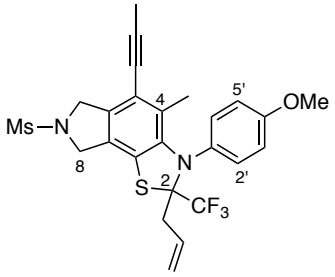
^{13}C NMR (125 MHz, $CDCl_3$): δ 171.9, 171.5, 166.9, 166.5, 146.4, 141.9, 140.1, 132.6, 131.1, 130.2, 130.0, 129.5, 129.43, 129.39, 129.36, 129.1, 127.7, 115.5, 95.5, 89.5, 71.9 (q, *J* = 34 Hz), 59.4, 55.0, 53.2 (2x), 52.22, 52.18, 40.9, 40.7, 31.7, 29.1, 29.0, 27.7, 26.3, 22.6, and 14.1. (The *C*F$_3$ carbon was not definitively detected.)

IR (neat): 2954, 2928, 2855, 2205, 1723 (br), 1606, 1560, 1508, 1436, 1398, 1376, 1307, 1276, 1197, 1173, 1118, 1074, 1019, and 964 cm^{-1}.

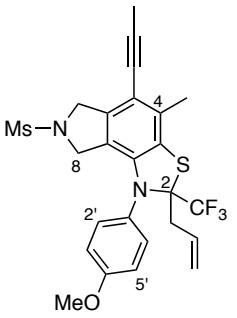
HRMS (ESI-TOF): Calculated for $C_{41}H_{43}F_3NO_8S^+$ [M+H$^+$] 766.2656, found 766.2636.

TLC: R_f 0.1 (6:1 hexanes:EtOAc).

2-Allyl-1-(4-methoxyphenyl)-4-methyl-7-(methylsulfonyl)-5-(prop-1-yn-1-yl)-2-(trifluoromethyl)-1,6,7,8-tetrahydro-2*H*-thiazolo[4,5-*e*]isoindole (428') and 2-Allyl-3-(4-methoxyphenyl)-4-methyl-7-(methylsulfonyl)-5-(prop-1-yn-1-yl)-2-(trifluoromethyl)-3,6,7,8-tetrahydro-2*H*-thiazolo[5,4-*e*]isoindole (428)



428'



428

Prepared following General Experimental Procedure B. In order of elution (hexanes:EtOAc 5:1), the isoindole derivatives **428'** (13.5 mg) and **428** (20.1 mg) were isolated in 24% and 36% yield, each as a white amorphous solid.

Compound 428'

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (dd, *J* = 8.8, 2.6 Hz, 1H, *H2'*), 6.92 (dd, *J* = 8.8, 2.9 Hz, 1H, *H6'*), 6.74 (dd, *J* = 8.8, 3.0 Hz, 1H, *H3'* or H5'), 6.70 (dd, *J* = 8.7, 2.6 Hz, 1H, *H5'* or H3'), 5.62 (dddd, *J* = 17.0, 10.3, 7.0, 7.0 Hz, 1H, CH_2=C*H*CH_2), 5.01 (dddd, *J* = 10.2, 1.1, 1.1, 1.1 Hz, 1H, C*H*$_a$H$_b$=CHCH_2), 4.96 (dddd, *J* = 16.8, 1.1, 1.1, 1.1 Hz, 1H, CH$_a$*H*$_b$=CHCH_2), 4.70 (ddd, *J* = 14.0, 2.1, 2.1 Hz, 1H, C8*H*$_a$H$_b$), 4.65 (ddd, *J* = 14.0, 2.1, 2.1 Hz, C8H$_a$*H*$_b$), 4.58 (m, 2H, C6*H*$_2$), 3.81 (s, 3H, OC*H*$_3$), 2.91 (s, 3H, C*H*$_3$S), 2.75 (dddd, *J* = 14.9, 6.7, 1.2, 1.2 Hz, 1H, CH_2=CHC*H*$_a$H$_b$), 2.50 (br dd, *J* = 15.0, 7.7 Hz, 1H, CH_2=CHCH$_a$*H*$_b$), 2.04 (s, 3H, C≡C-C*H*$_3$), and 1.77 (s, 3H, ArC*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.1, 147.5, 135.9, 134.7, 131.0, 130.5, 128.8, 127.3, 125.9, 125.3 (q, *J* = 285 Hz), 123.5, 120.0, 117.0, 114.36, 114.34, 94.1, 83.5 (q, *J* = 29 Hz), 75.3, 55.5, 54.4, 53.8, 37.1, 34.9, 16.7, and 4.5.

IR (neat): 2986, 2960, 2934, 2839, 2230, 1640, 1606, 1583, 1508, 1462, 1370, 1340, 1311, 1223, 1156, 1128, 1080, 1044, 1032, and 989 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{25}H_{26}F_3N_2O_3S_2^+$ [M+H$^+$] 523.1337, found 523.1333.

TLC: R_f 0.15 (5:1 hexanes:EtOAc).

Compound 428

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (dd, *J* = 8.8, 2.8 Hz, 1H, *H2'*), 7.01 (dd, *J* = 8.8, 2.7 Hz, 1H, *H6'*), 6.93 (dd, *J* = 8.6, 3.1 Hz, 1H, *H3'* or H5'), 6.83 (dd, *J* = 8.8, 3.1 Hz, 1H, *H5'* or H3'), 5.78 (dddd, *J* = 17.0, 10.0, 6.9, 6.9 Hz, 1H, CH_2=C*H*CH_2), 5.11 (dddd, *J* = 10.1, 1.0, 1.0, 1.0 Hz, 1H, C$H_a$$H_b$=C$HCH_2$), 5.04 (dddd, *J* = 16.9, 1.1, 1.1, 1.1 Hz, 1H, $CH_a$$H_b$=C$HCH_2$), 4.53 (m, 2H, C6$H_2$), 3.91 (br d, *J* = 13.9 Hz, 1H, C8$H_a$$H_b$), 3.84 (s, 3H, OC$H_3$), 3.44 (br d, *J* = 14.0 Hz, 1H, C8$H_a$$H_b$), 2.69 (s, 3H, C$H_3$S), 2.66 (br d, *J* = 7.0 Hz, 2H, CH_2=CHCH_2), 2.31 (s, 3H, ArCH_3), and 2.08 (s, 3H, C≡C-CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 141.1, 138.8, 132.3, 131.9, 131.5 (q, *J* = 2.0 Hz), 131.2, 130.6, 125.1 (q, *J* = 286 Hz), 124.9, 120.2, 116.8, 114.6, 114.5, 111.6, 92.9, 81.5 (q, *J* = 29 Hz), 75.0, 55.5, 53.9, 52.1, 37.2, 34.5, 18.8, and 4.6.

IR (neat): 3021, 3002, 2965, 2918, 2841, 2220, 1641, 1607, 1581, 1509, 1456, 1443, 1385, 1340, 1298, 1222, 1184, 1156, 1080, 1033, and 987 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{25}H_{26}F_3N_2O_3S_2^+$ [M+H^+] 523.1337, found 523.1333.

TLC: R_f 0.1 (5:1 hexanes:EtOAc).

Discussion of Computational Results

"DFT computations were performed with the Gaussian 09 software package.[132] The geometries were optimized with the M06-2X functional;[133] the basis set was double-ζ split-valence 6-311+G(d, p). The SMD continuum solvation model[134] with" benzene "as solvent was applied during both the frequency calculation and the geometry optimization. Harmonic vibrational frequency calculations were performed at 298 K and used for the thermal correction of enthalpies. The value for the 'Sum of electronic and thermal Free Energies=' was used to as the free energy (G) of the transition state structures (G_{TS}) as well as of the reactants and products. The optimized transition state structure geometry contained only one imaginary frequency."

Energies and Geometries of the species.

o-Benzyne (**101**)

Diethylthioamide **406a**

Ethylene

Ammonium ylide (zwitterion) **409**

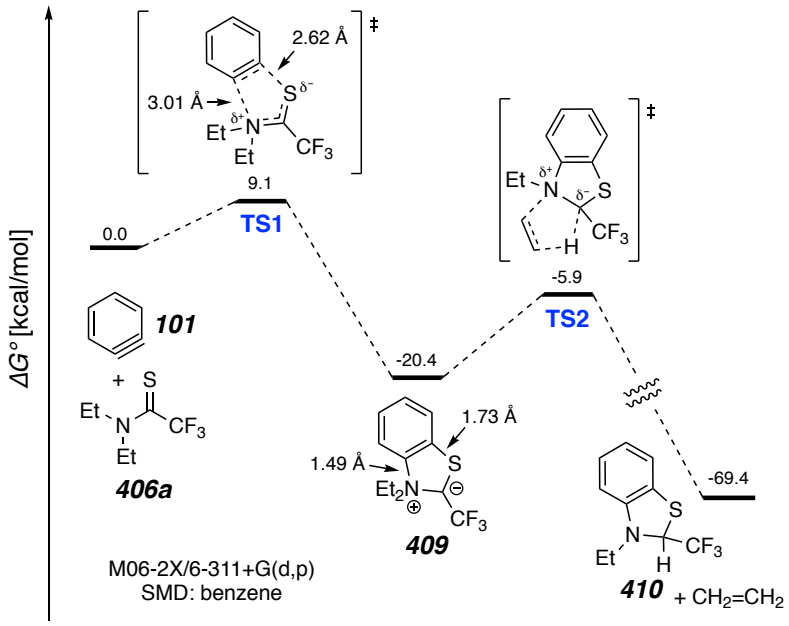
Dihydrobenzothiazole **410**

TS1 ([3+2] cycloaddition)

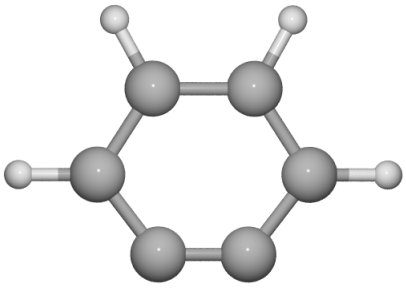
TS2 (elimination)

Thioacetamide **S7**

Ammonium ylide **S8**



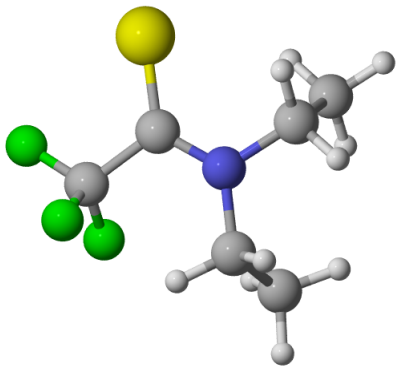
Geometry and free energy for benzyne (101)



Sum of electronic and thermal Free Energies = -230.819419 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.000004	-1.230476	0.619797
2	6	0	0.000004	-1.230476	-0.619797
3	6	0	-0.000002	-0.132275	-1.460441
4	6	0	-0.000002	1.051532	-0.702315
5	6	0	-0.000002	1.051532	0.702315
6	6	0	-0.000002	-0.132275	1.460441
7	1	0	0.000000	-0.134192	-2.541602
8	1	0	-0.000001	2.001507	-1.225681
9	1	0	-0.000001	2.001507	1.225681
10	1	0	0.000000	-0.134192	2.541602

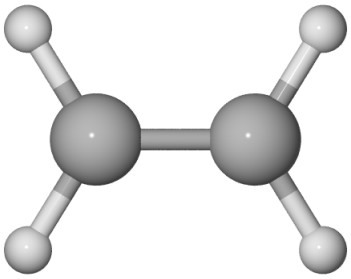
Geometry and free energy for diethylthioamide 406a



Sum of electronic and thermal Free Energies = -986.952362 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	16	0	-0.524687	2.173970	-0.043058
2	6	0	-0.311993	0.535778	-0.153435
3	6	0	-1.534802	-0.369970	0.089221
4	9	0	-1.915079	-0.980548	-1.046996
5	9	0	-2.583086	0.292125	0.544944
6	9	0	-1.256459	-1.330138	0.990302
7	7	0	0.825961	-0.096506	-0.446940
8	6	0	2.056613	0.693347	-0.622903
9	1	0	2.756612	0.060984	-1.170484
10	1	0	1.812812	1.555627	-1.245558
11	6	0	0.988951	-1.549064	-0.654971
12	1	0	0.021379	-2.023890	-0.765947
13	1	0	1.505389	-1.664302	-1.611240
14	6	0	1.783214	-2.210442	0.464190
15	1	0	1.830787	-3.285829	0.284868
16	1	0	2.805516	-1.832004	0.508184
17	1	0	1.301142	-2.039422	1.427999
18	6	0	2.666826	1.147793	0.699135
19	1	0	3.571979	1.723261	0.496290
20	1	0	1.973513	1.784600	1.246897
21	1	0	2.932921	0.295380	1.324841

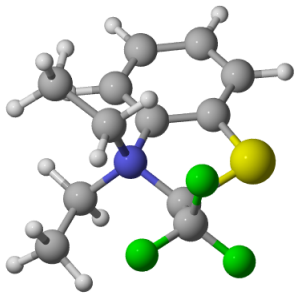
Geometry and free energy for ethylene



Sum of electronic and thermal Free Energies = -78.535101 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.663228	0.000000	0.000004
2	6	0	0.663228	0.000000	-0.000003
3	1	0	-1.231226	-0.923687	-0.000012
4	1	0	-1.231226	0.923687	0.000022
5	1	0	1.231226	0.923687	0.000010
6	1	0	1.231226	-0.923687	-0.000024

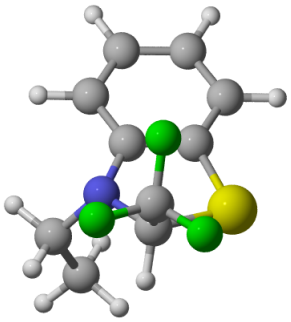
Geometry and free energy for the ammonium ylide (zwitterion) 409



Sum of electronic and thermal Free Energies = -1217.804265 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.813180	-1.669230	-0.023289
2	6	0	1.524037	-1.137386	-0.088397
3	6	0	1.347324	0.238026	-0.172637
4	6	0	2.436955	1.098020	-0.216372
5	6	0	3.720382	0.564508	-0.155480
6	6	0	3.903179	-0.812980	-0.050762
7	1	0	2.315930	2.169168	-0.297199
8	1	0	4.574327	1.228352	-0.193776
9	1	0	4.905171	-1.222246	-0.004832
10	16	0	0.049807	-2.045037	-0.107600
11	6	0	-0.900676	-0.545372	-0.600730
12	6	0	-2.226507	-0.699267	0.052635
13	9	0	-3.070082	0.339292	-0.140701
14	9	0	-2.284250	-0.902501	1.418491
15	9	0	-2.826855	-1.795966	-0.453937
16	7	0	-0.077155	0.681666	-0.160529
17	1	0	2.950429	-2.741866	0.034953
18	6	0	-0.428489	1.181885	1.241333
19	1	0	-1.497479	1.381772	1.227205
20	1	0	-0.252063	0.325174	1.891790
21	6	0	-0.215807	1.775942	-1.209869
22	1	0	0.467495	2.572694	-0.924034
23	1	0	0.145095	1.311936	-2.125506
24	6	0	0.318296	2.408403	1.733814
25	1	0	-0.080264	2.646361	2.722093
26	1	0	1.386843	2.232202	1.846055
27	1	0	0.154842	3.282193	1.101126
28	6	0	-1.604151	2.343853	-1.410895
29	1	0	-2.277689	1.606014	-1.837911
30	1	0	-2.038309	2.738293	-0.490823
31	1	0	-1.506815	3.173046	-2.114620

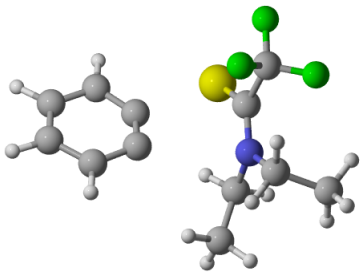
Geometry and free energy for dihydrobenzothiazole 410



Sum of electronic and thermal Free Energies = -1139.347304 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	2.308465	-1.495228	-0.629547
2	6	0	1.145353	-0.747581	-0.541342
3	6	0	1.019982	0.292221	0.384425
4	6	0	2.073530	0.587781	1.238328
5	6	0	3.249680	-0.155342	1.148233
6	6	0	3.367619	-1.188887	0.224882
7	1	0	1.973158	1.378091	1.972737
8	1	0	4.072919	0.069470	1.815163
9	1	0	4.282858	-1.765091	0.169067
10	16	0	-0.296862	-0.905911	-1.559632
11	6	0	-1.178450	0.271615	-0.449070
12	6	0	-2.140919	-0.482593	0.462903
13	9	0	-1.516381	-1.336610	1.274475
14	9	0	-3.042169	-1.174485	-0.248325
15	9	0	-2.821349	0.381708	1.230949
16	7	0	-0.211310	0.986047	0.349043
17	1	0	2.394740	-2.298347	-1.351151
18	6	0	-0.137170	2.438398	0.122130
19	1	0	0.490847	2.854990	0.910856
20	1	0	-1.139780	2.843029	0.274621
21	6	0	0.410094	2.812527	-1.251969
22	1	0	0.470061	3.897731	-1.353596
23	1	0	1.410735	2.396676	-1.391420
24	1	0	-0.230577	2.432900	-2.051720
25	1	0	-1.786016	0.949819	-1.051467

Geometry and free energy for TS1 ([3+2] cycloaddition)



Sum of electronic and thermal Free Energies = -1217.75726 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-3.124130	-1.055766	0.645861
2	6	0	-2.008228	-0.324776	0.307093
3	6	0	-1.836385	0.610332	-0.518741
4	6	0	-2.909810	1.079025	-1.280490
5	6	0	-4.122280	0.420732	-1.038345
6	6	0	-4.228153	-0.618766	-0.101096
7	1	0	-2.846522	1.880598	-2.008280
8	1	0	-5.007148	0.719446	-1.590715
9	1	0	-5.187654	-1.100525	0.052585
10	16	0	0.036887	-1.173622	1.699192
11	6	0	0.974108	-0.494867	0.501836
12	6	0	1.675140	-1.449273	-0.481240
13	9	0	1.125173	-1.368307	-1.702494
14	9	0	1.601918	-2.713789	-0.101041
15	9	0	2.983880	-1.158379	-0.606131
16	7	0	1.065078	0.803290	0.244924
17	1	0	-3.180768	-1.855367	1.372422
18	6	0	0.544376	1.770335	1.243683
19	1	0	-0.329624	1.315969	1.697242
20	1	0	1.308863	1.866874	2.023457
21	6	0	1.896007	1.388598	-0.827684
22	1	0	2.046843	0.659754	-1.615403
23	1	0	1.312127	2.196068	-1.266006
24	6	0	0.171918	3.127394	0.671316
25	1	0	-0.300289	3.702103	1.469685
26	1	0	1.028900	3.700686	0.315149
27	1	0	-0.553664	3.015551	-0.136470
28	6	0	3.228640	1.901173	-0.292878
29	1	0	3.800421	2.340752	-1.111763
30	1	0	3.087097	2.667876	0.470878
31	1	0	3.809726	1.084556	0.136785

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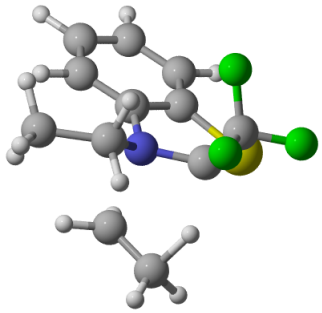
Geometry and free energy for TS2 (elimination)



Sum of electronic and thermal Free Energies = -1217.781143 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.616991	-1.675834	0.185140
2	6	0	-1.380079	-1.056175	0.281089
3	6	0	-1.192282	0.261193	-0.146227
4	6	0	-2.259745	0.970100	-0.680743
5	6	0	-3.498586	0.338593	-0.802233
6	6	0	-3.679534	-0.970196	-0.372604
7	1	0	-2.164698	1.994632	-0.998036
8	1	0	-4.326801	0.886928	-1.233518
9	1	0	-4.646986	-1.446602	-0.474242
10	16	0	0.089165	-1.725130	0.980687
11	6	0	1.051595	-0.340096	0.381445
12	6	0	2.003796	-0.721178	-0.698014
13	9	0	2.980575	0.192618	-0.902361
14	9	0	1.450432	-0.920379	-1.929408
15	9	0	2.624340	-1.868915	-0.385266
16	7	0	0.135203	0.747806	0.162679
17	1	0	-2.743083	-2.696534	0.524728
18	6	0	0.756514	1.842511	-0.648653
19	1	0	1.673764	2.076350	-0.106279
20	1	0	1.041608	1.424646	-1.615014
21	6	0	-0.012348	1.521186	1.992068
22	1	0	-0.193081	2.544464	1.691269
23	1	0	-0.907279	0.976493	2.276317
24	6	0	-0.035094	3.127342	-0.885326
25	1	0	0.689256	3.923293	-1.065417
26	1	0	-0.663320	3.063052	-1.771706
27	1	0	-0.650893	3.430738	-0.040177
28	6	0	1.235869	1.158364	2.578865
29	1	0	1.641841	0.385760	1.690030
30	1	0	1.964719	1.954253	2.705426
31	1	0	1.175066	0.485203	3.431329

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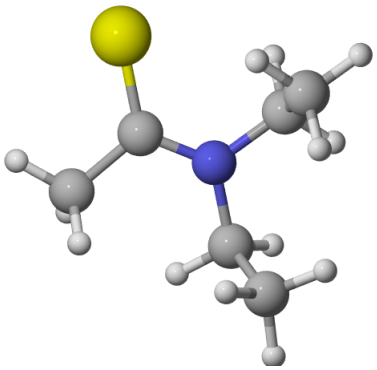
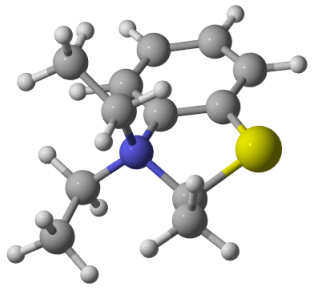
Geometry and free energy for *N,N*-diethyl thioacetamide S7



Sum of electronic and thermal Free Energies = -689.193466 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	16	0	2.241763	-0.298062	0.053081
2	6	0	0.824655	0.592545	-0.040550
3	7	0	-0.352393	0.070829	-0.407314
4	6	0	-0.491178	-1.365113	-0.686964
5	1	0	-1.400589	-1.483674	-1.279311
6	1	0	0.359168	-1.671050	-1.297712
7	6	0	-1.576615	0.864286	-0.571731
8	1	0	-1.321232	1.918876	-0.608066
9	1	0	-1.998759	0.608138	-1.547469
10	6	0	-2.601644	0.605373	0.527830
11	1	0	-3.460136	1.266048	0.394038
12	1	0	-2.961795	-0.424242	0.500111
13	1	0	-2.166535	0.793033	1.511901
14	6	0	-0.564893	-2.219345	0.575329
15	1	0	-0.674107	-3.269436	0.296572
16	1	0	0.348528	-2.113586	1.159214
17	1	0	-1.416826	-1.938242	1.195947
18	6	0	0.856357	2.068193	0.290749
19	1	0	1.829334	2.313787	0.703553
20	1	0	0.081777	2.330670	1.015634
21	1	0	0.699636	2.667234	-0.610483

Geometry and free energy for ammonium ylide S8



Sum of electronic and thermal Free Energies = -920.02145 a.u.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.720774	0.938107	-0.016998
2	6	0	-1.327645	0.882309	-0.019189
3	6	0	-0.688286	-0.341327	-0.207245
4	6	0	-1.411951	-1.505798	-0.415495
5	6	0	-2.803483	-1.442746	-0.422961
6	6	0	-3.450511	-0.226843	-0.214677
7	1	0	-0.922274	-2.458046	-0.571854
8	1	0	-3.376585	-2.344887	-0.594858
9	1	0	-4.533129	-0.184390	-0.222459
10	16	0	-0.216335	2.201366	0.177634
11	6	0	1.156518	1.191943	-0.579129
12	6	0	2.423445	1.717713	0.090029
13	7	0	0.788679	-0.270521	-0.087951
14	1	0	-3.220140	1.889141	0.121734
15	6	0	1.185238	-0.556049	1.348562
16	1	0	2.266084	-0.433386	1.392667
17	1	0	0.735391	0.251821	1.929111
18	6	0	1.402178	-1.259332	-1.045533
19	1	0	1.123522	-2.255859	-0.704422
20	1	0	0.915387	-1.061191	-1.998696
21	6	0	0.783252	-1.911087	1.907443
22	1	0	1.115334	-1.950825	2.947130
23	1	0	-0.296611	-2.056113	1.899953
24	1	0	1.260640	-2.741199	1.383859
25	6	0	2.908035	-1.176892	-1.208300
26	1	0	3.193118	-0.255965	-1.712394
27	1	0	3.446226	-1.260523	-0.262488
28	1	0	3.213889	-2.017383	-1.834346
29	1	0	2.409906	1.785814	1.189245
30	1	0	3.317259	1.167430	-0.204965
31	1	0	2.556507	2.737360	-0.282755

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Supplementary Information for Chapter 5

General Experimental Information

^{13}C and ^{1}H NMR spectra were measured on Bruker Avance spectrometers (500 or 400 MHz). ^{13}C and ^{1}H NMR chemical shifts for spectra recorded in $CDCl_3$ are referenced to TMS (δ 0.00 ppm). Some of the carbon spectra contain a resonance at ca. 100.0 ppm which is an artifact of the data collection. Non-first order multiplets in ^{1}H NMR spectra are designated "nfom". This format is used for reporting resonances: chemical shift in ppm [multiplicity, coupling constant(s) (*J* in Hz), integral (to the nearest whole proton), and substructural assignment]. ^{1}H NMR assignments are designated by the neighboring atoms (e.g., C*H*OH). Analysis of coupling constants was performed using methods we have reported earlier.[130,131]

Infrared spectra were collected as thin film samples on either a Nicolet iS5 or a Bruker Alpha II spectrometer, the latter in ATR mode.

HRMS were collected on either i) a Thermo Orbitrap Velos in electron spray ionization (ESI), positive mode [sample introduction as a dilute solution in methanol; external standard (Pierce™ LTQ); mass accuracy < 4 ppm]. or ii) a Bruker BioTOF II (ESI-TOF) instrument in electrospray ionization (ESI) mode [PEG as an added internal standard/calibrant; sample introduction as a dilute solution in methanol]. In the latter instance, the HRMS data were collected as multiple individual measurements from which the median value from a total of eleven measured values is reported.

GCMS data were obtained on an Agilent 5975 mass spectrometer in electron ionization (EI) mode at 70 eV. The GC column (15 m × 0.25 mm) contained a DB5 stationary phase of 25 μM film thickness. The temperature program used was isothermal for 50 °C for 1.5 min followed by a 20 °C/min ramp to 250 °C.

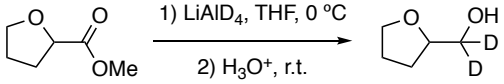
Medium pressure liquid chromatography (MPLC) was performed at 25-200 psi on dry-packed columns of silica gel (25-35 μm, 60 Å pore size). A Waters HPLC pump (M6000) was used at flow rates of ca. 6 $mL \bullet min^{-1}$. A Waters R401 differential refractive index (RI) detector was used to monitor the eluent. Flash chromatography was carried using E. Merck silica gel (230-400 mesh). Thin layer chromatography was done on plastic-backed plates coated with silica gel. Plates were visualized by UV detection and, subsequently, by dipping into a solution of basic potassium permanganate.

Reaction temperatures refer to the temperature of the external heating or cooling bath. HDDA reactions, were typically performed in a vial or culture tube fitted with an inert, Teflon®-lined, threaded cap.All of the epoxy-containing alcohol trapping agents used are known compounds. The spectral data for the samples we prepared were consistent with those reported in the literature for each.

General Experimental Procedure A

A solution of polyyne substrate and trapping agent (3 molar equiv.) in 8 mL of 1,2-dichloroethane (pre-treated by passage through a plug of solid K_2CO_3) ($[polyyne]_0$ = 0.01–0.02 M) was heated in a screw-capped culture tube in an oil bath held at ca. 85 °C. In the case of synthesis of **533**, **534** and **535**, ethyl acetate was used as the reaction solvent instead of 1,2-dichloroethane. After 16 h the solution was allowed to cool to ambient temperature and directly passed through a plug of silica gel (EtOAc elution). The effluent was concentrated and the resulting residue was purified by MPLC in the indicated elution solvent to give the indicated product(s). The scale of most of these reactions was ca. 0.1 mmol. In the case of **533**, **534** and **535**, the reaction was also performed on a 1 mmol scale. In the case of synthesis of **521** from cyclopropanol **501f** (14.3 mg, 0.112 mmol, 2.76 equiv.), $CDCl_3$ (2 mL) was used as the reaction solvent.

(Tetrahydrofuran-2-yl)methan-*d*2-ol (501b-*d*$_2$)



To a stirred slurry of $LiAlD_4$ (459 mg, 11.6 mmol) in dry THF (8 mL) was added a solution of methyl tetrahydrofuroate (300 mg, 2.32 mmol) in dry THF (2 mL) dropwise at 0 ºC. The reaction mixture was allowed to warm to ambient temperature and stirred overnight. The mixture was then worked up using standard Fieser-Fieser method[137] and was extracted 3 times with ether. The combined organic layer was concentrated to provide compound **501b-*d*$_2$** (162 mg) in 67% yield. Analysis of the proton NMR spectrum indicated this sample to contain ca. 9% THF and only trace levels (<1%) of any other components. The level of deuteration was judged to be 96% d_2, 4% d_1, and 0% d_0 from the proton NMR spectrum. [Analysis of the electron ionization mass spectrum fragmentation patterns clearly indicated that **501b-*d*$_2$** was, by far, the dominant product, but it was not possible to quantify the level of deuteration; the molecular ion (*m/z* = 104) for this compound was only 0.2% of the base peak (*m/z* = 71), and the deuterium-containing fragment ions were confounded by nearby inherent fragments differing by one or two mass units.]

Compound 501b-*d*$_2$

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.01 (br t, J = 7 Hz, 1H, *H2*), 3.87 (nfom, ΣJ = 21 Hz (and includes an 8.5 Hz J_{gem}), 1H, *H5a*), 3.80 (nfom, ΣJ = 22 Hz (and includes an 8.5 Hz J_{gem}), 1H, *H5b*), 2.07 (br s, 1H, O*H*), 1.96–1.87 (m, 3H, , *H3* or *H4*), and 1.69–1.62 (nfom, 1H, *H3* or *H4*).

^{13}C NMR (125 MHz, $CDCl_3$): 79.2, 68.3, 27.1, and 26.1. The resonance at ca. 64.5 for the carbinol carbon in the all protio analog, now coupled to deuterium atoms, is not discernable in the spectrum.

IR (neat): 3406, 2952, 2870, 2204, 2091, 1459, 1355, 1300, 1240, 1182, 1157, 1111, 1067, 1037, 965, and 919 cm^{-1}.

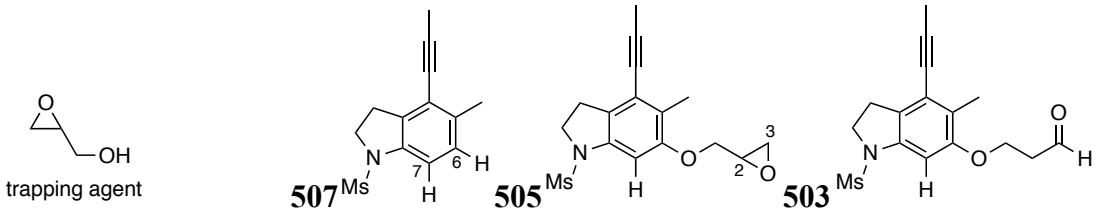
GC-MS (EI, 70 eV): t_R = 1.90 min. Calculated for $C_5H_8D_2O_2^+$ [M^+] 104, found 104.

[137] Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis* Vol. 1. Wiley; New York: **1967**. pp 581–595.

5-Methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indoline (507),

3-((5-Methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)oxy)propanal (505) and

5-Methyl-1-(methylsulfonyl)-6-(oxiran-2-ylmethoxy)-4-(prop-1-yn-1-yl)indoline (503)



Prepared following General Experimental Procedure A. Polyyne substrate: **215** (30.0 mg, 0.121 mmol). Trapping agent: glycidol (26.9 mg, 0.364 mmol). In order of elution (hexanes:EtOAc 3:1), the indoline derivatives **507** (0.8 mg), **505** (9.0 mg), and **503** (25.7 mg) were isolated in 2%, 23%, and 66% yield, respectively, each as a white crystalline solid.

Compound 507

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.4 Hz, 1H, *H7*), 7.04 (dq, *J* = 8.4, 0.7 Hz, 1H, *H6*), 3.99 (app t, *J* = 8.4 Hz, 2H, N*CH*$_2$CH$_2$), 3.19 (app t, *J* = 8.5 Hz, 2H, NCH$_2$*CH*$_2$), 2.85 (s, 3H, O_2SCH_3), 2.38 (br s, 3H, Ar*CH*$_3$), and 2.15 (s, 3H, ≡CC*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 139.5, 135.4, 134.0, 128.7, 121.3, 112.9, 94.1, 75.8, 50.4, 34.1, 28.2, 19.9, and 4.6.

IR (neat): 3015, 2916, 2851, 2235, 1604, 1582, 1469, 1379, 1336, 1246, 1228, 1149, 1090, 1050, 1006, and 973 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{13}H_{16}NO_2S^+$ [M+H$^+$] 250.0902, found 250.0893.

TLC: R_f 0.3 (2:1 hexanes:EtOAc).

mp: 135–138 °C.

Compound 505

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.94 (s, 1H, Ar*H*), 4.27 (dd, *J* = 11.1, 2.6 Hz, 1H, C1*H*$_a$H$_b$), 3.99-3.93 (m, 2H, N*CH*$_2$CH$_2$), 3.90 (dd, *J* = 11.3, 5.9 Hz, 1H, C1H$_a$*H*$_b$), 3.35 (dddd, *J* = 5.6, 4.2, 2.7, 2.7 Hz, 1H, C2*H*), 3.11 (app t, *J* = 8.4 Hz, 2H, NCH$_2$*CH*$_2$), 2.90 (dd, *J* = 4.9, 4.3 Hz, 1H, C3*H*$_a$H$_b$), 2.82 (s, 3H, O_2SCH_3), 2.77 (dd, *J* = 4.9, 2.7 Hz, 1H, C3H$_a$*H*$_b$), 2.28 (s, 3H, Ar*CH*$_3$), and 2.12 (s, 3H, ≡CC*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.4, 139.8, 125.8, 124.5, 121.9, 98.8, 93.9, 75.9, 69.4, 50.7, 50.2, 44.4, 34.1, 27.8, 13.6, and 4.5.

IR (neat): 2987, 2920, 2859, 1592, 1477, 1452, 1422, 1349, 1314, 1214, 1161, 1147, 1099, 1063, 1021, and 968 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{16}H_{20}NO_4S^+$ $[M+H^+]$ 322.1113, found 322.1104.

TLC: R_f 0.25 (2:1 hexanes:EtOAc).

mp: 161–164 °C.

Compound 503

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.87 (t, *J* = 1.8 Hz, 1H, C*H*O), 6.97 (s, 1H, Ar*H*), 4.31 (t, *J* = 5.9 Hz, 2H, O*CH*$_2$CH$_2$), 3.97 (t, *J* = 8.3 Hz, 2H, N*CH*$_2$CH$_2$), 3.11 (t, *J* = 8.5 Hz, 2H, NCH$_2$*CH*$_2$), 2.89 (td, *J* = 5.8, 1.7 Hz, 2H, OCH$_2$*CH*$_2$), 2.83 (s, 3H, O$_2$SC*H*$_3$), 2.20 (s, 3H, ArC*H*$_3$), and 2.11 (s, 3H, ≡CC*H*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 200.0, 156.3, 139.9, 125.8, 124.4, 121.9, 98.7, 93.9, 75.9, 62.5, 50.7, 43.2, 34.2, 27.8, 13.5, and 4.5.

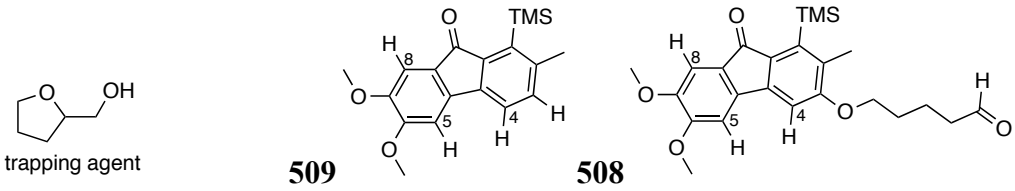
IR (neat): 2986, 2920, 2835, 2224, 1727, 1591, 1505, 1477, 1455, 1422, 1392, 1349, 1211, 1161, 1099, 1053, and 969 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{16}H_{20}NO_4S^+$ $[M+H^+]$ 322.1113, found 322.1106.

TLC: R_f 0.2 (2:1 hexanes:EtOAc).

mp: 143–146 °C.

6,7-Dimethoxy-2-methyl-1-(trimethylsilyl)-9*H*-fluoren-9-one (509) and 5-((6,7-Dimethoxy-2-methyl-9-oxo-1-(trimethylsilyl)-9*H*-fluoren-3-yl)oxy)pentanal (508)



Prepared following General Experimental Procedure A. Polyyne substrate: **226** (30.0 mg, 0.0924 mmol). Trapping agent: (tetrahydrofuran-2-yl)methanol (28.3 mg, 0.277 mmol). In order of elution (hexanes:EtOAc 2:1), the fluorenone derivatives **509** (5.2 mg) and **508** (24.9 mg) were isolated in 10% and 48% yield, each as an orange amorphous solid.

Compound 509

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (d, *J* = 7.5 Hz, 1H, *H4*), 7.13 (s, 1H, *H8*), 7.12 (dq, *J* = 7.5, 0.8 Hz, 1H, *H3*), 6.93 (s, 1H, *H5*), 4.00 (s, 3H, C7OCH_3), 3.91 (s, 3H, C6OCH_3), 2.44 (br s, 3H, ArCH_3), and 0.44 [s, 9H, Si(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 194.7, 154.4, 149.4, 144.1, 142.2, 140.8, 140.7, 139.1, 135.0, 126.5, 119.5, 106.9, 102.6, 56.3, 56.2, 25.1, and 2.6.

IR (neat): 3006, 2950, 2901, 2838, 1705, 1601, 1585, 1492, 1464, 1442, 1421, 1377, 1342, 1319, 1242, 1215, 1150, 1113, 1048, 1021, and 995 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{19}H_{23}O_3Si^+$ [M+H$^+$] 327.1416, found 327.1406.

TLC: R_f 0.3 (2:1 hexanes:EtOAc).

Compound 508

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.82 (t, *J* = 1.5 Hz, 1H, C*H*O), 7.10 (s, 1H, *H8*), 6.92 (s, 1H, *H5 or H4*), 6.84 (s, 1H, *H4 or H5*), 4.11 (t, *J* = 5.6 Hz, 2H, OCH_2), 4.01 (s, 3H, C7OCH_3), 3.90 (s, 3H, C6OCH_3), 2.58 (td, *J* = 6.8, 1.5 Hz, 2H, CH_2CHO), 2.28 (s, 3H, ArCH_3), 1.94–1.84 (m, 4H, OCH$_2$(CH_2)$_2$CH$_2$), and 0.42 [s, 9H, Si(CH_3)$_3$].

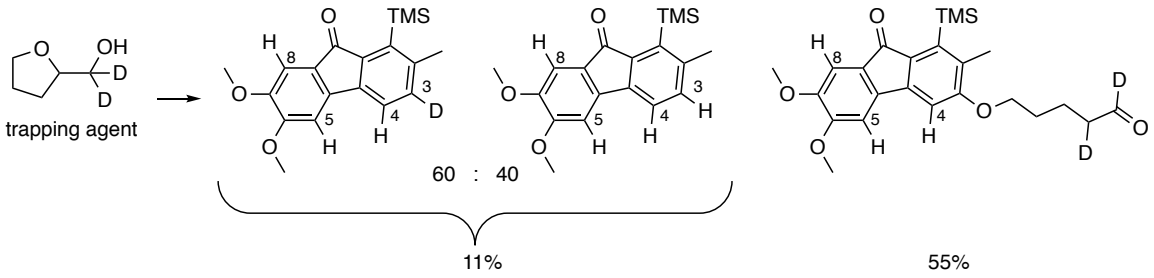
^{13}C NMR (125 MHz, $CDCl_3$): δ 202.0, 193.6, 160.7, 153.8, 149.4, 145.3, 142.9, 137.9, 132.2, 131.8, 127.4, 106.7, 103.1, 102.5, 67.8, 56.4, 56.2, 43.4, 28.7, 18.9, 16.7, and 2.7.

IR (neat): 3005, 2948, 2899, 2835, 2727, 1722, 1700, 1585, 1557, 1496, 1470, 1443, 1417, 1350, 1312, 1235, 1216, 1183, 1150, 1092, 1016, and 991 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{24}H_{31}O_5Si^+$ [M+H$^+$] 427.1941, found 427.1925.

TLC: R_f 0.1 (2:1 hexanes:EtOAc).

6,7-Dimethoxy-2-methyl-1-(trimethylsilyl)-9*H*-fluoren-9-one-3-*d* (509-*d*$_1$) and 5-((6,7-Dimethoxy-2-methyl-9-oxo-1-(trimethylsilyl)-9*H*-fluoren-3-yl)oxy)pentanal-1,2-*d*$_2$ (508-*d*$_2$)



Prepared following General Experimental Procedure A. Polyyne substrate: **226** (30.0 mg, 0.0924 mmol). Trapping agent: (tetrahydrofuran-2-yl)methan-*d*$_2$-ol (28.9 mg, 0.277 mmol). In order of elution (hexanes:EtOAc 2:1), the fluorenone derivatives **509-*d*$_1$/509** (5.5 mg) and **508-*d*$_2$** (28.3 mg) were isolated in 11% and 55% yield, each as an orange amorphous solid.

Compound 509-*d*$_1$

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.230 (d, *J* = 7.5 Hz, 0.4H, *H4* in **509**); 7.229 (s, 0.6H, *H4* in **509-*d*$_1$**), 7.13 (s, 1H, *H8*), 7.12 (dq, *J* = 7.5, 0.8 Hz, 0.5H, *H3* in **509**), 6.93 (s, 1H, *H5*), 4.00 (s, 3H, C7OC*H*$_3$), 3.91 (s, 3H, C6OC*H*$_3$), 2.44 (s, 3H, ArC*H*$_3$), and 0.42 [s, 9H, Si(C*H*$_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 194.7, 154.4, 149.4, 144.09 (ca 0.5C), 144.01 (ca 0.5C), 142.2, 140.8, 140.7, 139.1, 135.0, 126.5, 119.5 (ca. 0.5C), 119.4 (ca 0.5C), 106.9, 102.6, 56.3, 56.2, 25.13 (ca. 0.5C), 25.06 (ca. 0.5C), and 2.6.

IR (neat): 3008, 2985, 2951, 2901, 2838, 1705, 1601, 1584, 1555, 1495, 1471, 1421, 1373, 1347, 1317, 1244, 1215, 1153, 1111, 1048, 1029, and 998 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{19}H_{22}DO_3Si^+$ [M+H$^+$] 328.1479, found 328.1470.

TLC: R_f 0.3 (2:1 hexanes:EtOAc).

Compound 508-*d*$_2$

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10 (s, 1H, *H8*), 6.92 (s, 1H, *H5 or H4*), 6.84 (s, 1H, *H4 or H5*), 4.10 (t, *J* = 5.8 Hz, 2H, OC*H*$_2$), 4.01 (s, 3H, C7OC*H*$_3$), 3.90 (s, 3H, C6OC*H*$_3$), 2.55 (tt, *J* = 7.1, 2.5 Hz, 1H, C*H*DCDO), 2.29 (s, 3H, ArC*H*$_3$), 1.95–1.83 (m, 4H, OCH$_2$(*CH*$_2$)$_2$CHD), and 0.42 [s, 9H, Si(C*H*$_3$)$_3$].

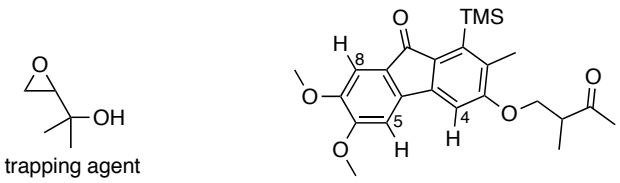
^{13}C NMR (125 MHz, $CDCl_3$): δ 201.8 (t, J = 26 Hz), 193.6, 160.7, 153.8, 149.4, 145.3, 142.9, 137.9, 132.2, 131.8, 127.4, 106.7, 103.1, 102.5, 67.8, 56.4, 56.2, 42.9 (tt, J = 18, 4 Hz), 28.7, 18.9, 16.7, and 2.7.

IR (neat): 3006, 2983, 2946, 2901, 2838, 2087, 1701, 1585, 1557, 1496, 1470, 1443, 1418, 1387, 1350, 1235, 1216, 1182, 1150, 1093, 1016, and 992 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{24}H_{29}D_2O_5Si^+$ [$M+H^+$] 429.2067, found 429.2051.

TLC: R_f 0.1 (2:1 hexanes:EtOAc).

6,7-Dimethoxy-2-methyl-3-(2-methyl-3-oxobutoxy)-1-(trimethylsilyl)-9*H*-fluoren-9-one (512)



Prepared following General Experimental Procedure A. Polyyne substrate: **226** (30.0 mg, 0.0924 mmol). Trapping agent: 2-(oxiran-2-yl)propan-2-ol (28.3 mg, 0.277 mmol). The fluorenone derivative **512** (26.2 mg) was isolated by MPLC (hexanes:EtOAc 2:1) in 51% yield and as an orange amorphous solid.

Compound 512

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (s, 1H, *H8*), 6.93 (s, 1H, *H5 or H4*), 6.87 (s, 1H, *H4 or H5*), 4.29 (dd, *J* = 8.9, 6.7 Hz, 1H, OC*H*$_a$H$_b$), 4.09 (dd, *J* = 9.0, 6.2 Hz, 1H, OCH$_a$*H*$_b$), 4.02 (s, 3H, C7OC*H*$_3$), 3.90 (s, 3H, C6OC*H*$_3$), 3.13 (ddq, *J* = 7.0, 7.0, 7.0 Hz, 1H, C*H*CH$_3$), 2.30 (s, 3H, ArC*H*$_3$), 2.25 (s, 3H, C(O)C*H*$_3$), 1.31 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$), and 0.41 [s, 9H, Si(C*H*$_3$)$_3$].

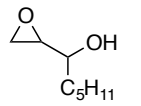
^{13}C NMR (125 MHz, $CDCl_3$): δ 210.2, 193.6, 160.4, 153.9, 149.5, 145.3, 143.0, 137.9, 132.5, 131.7, 127.3, 106.7, 103.3, 102.6, 69.8, 56.4, 56.2, 46.6, 29.2, 16.6, 13.8, and 2.7.

IR (neat): 2981, 2941, 2900, 2837, 1702, 1585, 1559, 1496, 1465, 1418, 1387, 1350, 1312, 1235, 1216, 1180, 1150, 1092, 1017, 1002, and 988 cm^{-1}.

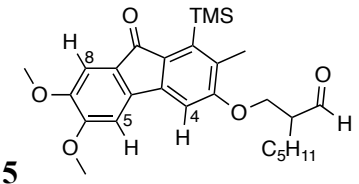
HRMS (ESI-TOF): Calculated for $C_{24}H_{31}O_5Si^+$ [M+H$^+$] 427.1941, found 427.1924.

TLC: R_f 0.1 (2:1 hexanes:EtOAc).

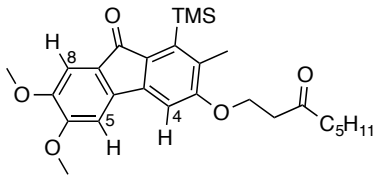
2-(((6,7-Dimethoxy-2-methyl-9-oxo-1-(trimethylsilyl)-9*H*-fluoren-3-yl)oxy)methyl)heptanal (515) and 6,7-Dimethoxy-2-methyl-3-((3-oxooctyl)oxy)-1-(trimethylsilyl)-9*H*-fluoren-9-one (516)



trapping agent



515



516

Prepared following General Experimental Procedure A. Polyyne substrate: **226** (30.0 mg, 0.0924 mmol). Trapping agent: 1-(oxiran-2-yl)hexan-1-ol (40.0 mg, 0.277 mmol). In order of elution (hexanes:EtOAc 2:1), the fluorenone derivatives **515** (18.0 mg) and **516** (19.7 mg) were isolated in 32% and 35% yield, each as an orange amorphous solid.

Compound 515

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.83 (d, *J* = 1.7 Hz, 1H, C*H*O), 7.11 (s, 1H, *H8*), 6.93 (s, 1H, *H5 or H4*), 6.89 (s, 1H, *H4 or H5*), 4.35 (dd, *J* = 9.3, 6.2 Hz, 1H, OCH_aH$_b$), 4.27 (dd, *J* = 9.3, 5.3 Hz, 1H, OCH$_a$$H_b$), 4.02 (s, 3H, C6OC$H_3$), 3.91 (s, 3H, C7OC$H_3$), 2.85 (dddt, *J* = 6, 6, 6, 1.8 Hz, 1H, C*H*CHO), 2.24 (s, 3H, ArCH_3), 1.89 (nfom, Σ*J* = 37 Hz, 1H, CHCH_aH$_b$), 1.72 (nfom, Σ*J* = 36 Hz, 1H, CHCH$_a$$H_b$), 1.49–1.40 [m, 2H, CH_2], 1.39–1.30 [m, 4H, (CH_2)$_2$CH$_3$], 0.91 [t, *J* = 7.0 Hz, 3H, (CH$_2$)$_3$CH_3], and 0.41 [s, 9H, Si(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 202.8, 193.6, 160.2, 153.9, 149.5, 145.2, 143.1, 137.8, 132.7, 132.0, 127.3, 106.8, 103.2, 102.5, 66.5, 56.4, 56.2, 51.5, 31.8, 26.5, 26.0, 22.4, 16.6, 14.0, and 2.7.

IR (neat): 2986, 2958, 2934, 2860, 2727, 1725, 1702, 1585, 1559, 1496, 1465, 1442, 1421, 1393, 1349, 1312, 1235, 1217, 1150, 1092, 1016, and 895 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{27}H_{37}O_5Si^+$ [M+H$^+$] 469.2411, found 469.2401.

TLC: R_f 0.15 (2:1 hexanes:EtOAc).

Compound 516

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (s, 1H, *H8*), 6.94 (s, 1H, *H5 or H4*), 6.91 (s, 1H, *H4 or H5*), 4.36 (t, *J* = 6.6 Hz, 2H, OCH_2), 4.02 (s, 3H, C6OCH_3), 3.90 (s, 3H, C7OCH_3), 2.98 (t, *J* = 6.4 Hz, 2H, OCH$_2$CH_2), 2.53 [t, *J* = 7.4 Hz, 2H, C(O)CH_2(CH$_2$)$_3$], 2.23 (s, 3H, ArCH_3), 1.64 [quintet, *J* = 7.4 Hz, 2H, C(O)CH$_2$(CH_2)CH$_2$], 1.38–1.28 [m, 4H, (CH_2)$_2$CH$_3$], 0.91 [t, *J* = 6.9 Hz, 3H, (CH$_2$)$_3$CH_3], and 0.41 [s, 9H, Si(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 208.8, 193.7, 160.5, 153.9, 149.5, 145.3, 142.9, 137.9, 132.5, 131.7, 127.3, 106.7, 103.4, 102.6, 63.7, 56.4, 56.2, 43.7, 42.0, 31.4, 23.4, 22.5, 16.6, 13.9, and 2.7.

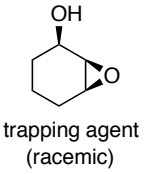
IR (neat): 2985, 2958, 2940, 2873, 1702, 1586, 1558, 1496, 1465, 1442, 1420, 1386, 1350, 1312, 1236, 1216, 1181, 1150, 1092, 1016, and 991 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{27}H_{37}O_5Si^+$ $[M+H^+]$ 469.2411, found 469.2395.

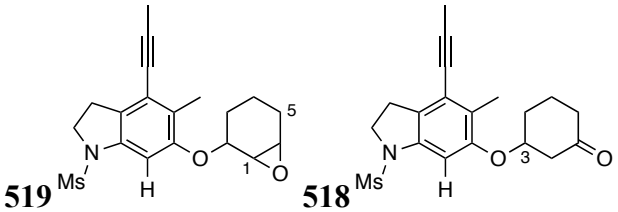
TLC: R_f 0.1 (2:1 hexanes:EtOAc).

6-((7-Oxabicyclo[4.1.0]heptan-2-yl)oxy)-5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indoline (519) and

3-((5-Methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)oxy)cyclohexan-1-one (518)



trapping agent
(racemic)



Prepared following General Experimental Procedure A. Polyyne substrate: **215** (30.0 mg, 0.121 mmol). Trapping agent: *cis*-7-oxabicyclo[4.1.0]heptan-2-ol (41.5 mg, 0.364 mmol). In order of elution (hexanes:EtOAc 2:1), the indoline derivatives **519** (6.5 mg) and **518** (21.6 mg) were isolated in 15% and 49% yield, each as a white amorphous solid.

Compound 519

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.08 (s, 1H, Ar*H*), 4.58 (ddd, *J* = 8.8, 5.5, 2.1 Hz, 1H, *H2*), 3.97 (t, *J* = 8.4 Hz, 2H, N*CH*$_2$CH$_2$), 3.36 (ddd, *J* = 4.2, 2.1, 0.7 Hz, 1H, *H1*), 3.30 (dddd, *J* = 4, 3, 1.8, 1.0 Hz, 1H, *H6*), 3.12 (t, *J* = 8.4 Hz, 2H, NCH$_2$*CH*$_2$), 2.82 (s, 3H, O$_2$SC*H*$_3$), 2.30 (s, 3H, ArC*H*$_3$), 2.11 (s, 3H, ≡CC*H*$_3$), 1.89–1.84 [m, 2H, (C*H*$_2$)$_3$], 1.76–1.61 [m, 3H, (C*H*$_2$)$_3$], and 1.38–1.24 [m, 1H, (C*H*$_2$)$_3$]. HSQC and HMBC were also used to make this assignment.

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.5, 139.8, 126.46, 126.45, 122.1, 101.5, 93.9, 76.0, 75.7, 54.4, 53.1, 50.7, 34.1, 27.9, 25.0, 22.8, 19.5, 13.9, and 4.6.

IR (neat): 2987, 2953, 2921, 2853, 1592, 1551, 1477, 1457, 1421, 1381, 1349, 1317, 1218, 1161, 1097, 1064, 1022, 995, and 968 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{19}H_{24}NO_4S^+$ [M+H$^+$] 362.1426, found 362.1416.

TLC: R_f 0.2 (2:1 hexanes:EtOAc).

Compound 518

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.93 (s, 1H, Ar*H*), 4.82 (dddd, *J* = 4.9, 4.9, 4.9, 2.7 Hz, 1H, *H3*), 3.98 (ddd, *J* = 10.8, 9.0, 7.6 Hz, 1H, N*CHa*Hb), 3.95 (ddd, *J* = 10.7, 8.8, 7.8 Hz, 1H, NCHa*Hb*), 3.12 (ddd, *J* = 16.7, 8.0, 8.0 Hz, 1H, Ar*CHa*Hb), 3.11 (ddd, *J* = 16.3, 8.5, 8.5 Hz, 1H, ArCHa*Hb*), 2.82 (s, 3H, O$_2$SC*H*$_3$), 2.65$^+$ (dd, *J* = 15, 4.6 Hz, 1H, C2*Ha*Hb), 2.65$^-$ (dd, *J* = 15, 4.6 Hz, 1H, C2Ha*Hb*), 2.48–2.34 [m, 2H, (C*H*$_2$)$_3$], 2.19 (s, 3H, ArC*H*$_3$),

2.11 (s, 3H, ≡CC*H*$_3$), 2.11–1.97 [m, 3H, (C*H*$_2$)$_3$], and 1.89–1.81 [m, 1H, (C*H*$_2$)$_3$]. HSQC and HMBC were also used to make this assignment.

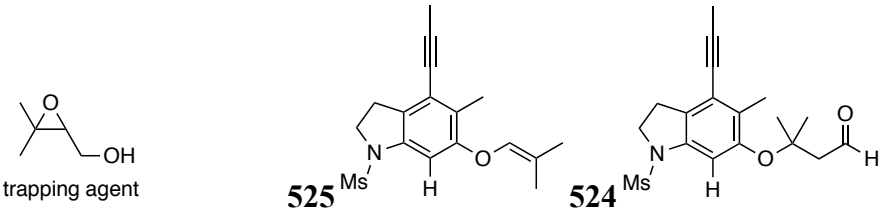
^{13}C NMR (125 MHz, $CDCl_3$): δ 208.7, 154.5, 139.8, 126.3, 125.6, 122.3, 100.5, 94.0, 75.9, 75.4, 50.6, 46.6, 41.1, 34.2, 29.1, 27.9, 20.6, 13.7, and 4.5.

IR (neat): 2986, 2953, 2920, 2879, 2859, 2231, 1716, 1592, 1477, 1443, 1382, 1349, 1224, 1209, 1161, 1139, 1097, 1090, 1026, and 970 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{19}H_{24}NO_4S^+$ [M+H$^+$] 362.1426, found 362.1417.

TLC: R_f 0.1 (2:1 hexanes:EtOAc).

5-Methyl-6-((2-methylprop-1-en-1-yl)oxy)-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indoline (525) and 3-Methyl-3-((5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)oxy)butanal (524)



Prepared following General Experimental Procedure A. Polyyne substrate: **225** (30.0 mg, 0.121 mmol). Trapping agent: (3,3-dimethyloxiran-2-yl)methanol (37.1 mg, 0.364 mmol). In order of elution (hexanes:EtOAc 3:1), the indoline derivatives **525** (15.2 mg) and **524** (9.1 mg) were isolated in 36% and 21% yield, each as a white crystalline solid.

Compound 525

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.97 (s, 1H, Ar*H*), 6.16 (septet, *J* = 1.5 Hz, 1H, C=C*H*), 3.96 (t, *J* = 8.6 Hz, 2H, N*CH*$_2$CH$_2$), 3.12 (t, *J* = 8.5 Hz, 2H, NCH$_2$*CH*$_2$), 2.83 (s, 3H, O$_2$SC*H*$_3$), 2.29 (s, 3H, ArC*H*$_3$), 2.12 (s, 3H, ≡CC*H*$_3$), 1.72 (d, *J* = 1.2 Hz, 3H, C=CC*Ha*$_3$CHb$_3$), and 1.68 (d, *J* = 1.2 Hz, 3H, C=CCHa$_3$C*Hb*$_3$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 155.7, 139.8, 135.3, 126.7, 124.5, 122.0, 117.3, 100.8, 93.9, 75.9, 50.7, 34.2, 27.9, 19.5, 15.3, 13.5, and 4.6.

IR (neat): 2957, 2919, 2884, 2857, 1687, 1600, 1592, 1510, 1477, 1456, 1421, 1383, 1349, 1315, 1163, 1111, 1085, 1061, 1028, and 968 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{17}H_{22}NO_3S^+$ [M+H$^+$] 320.1320, found 320.1311.

TLC: R_f 0.3 (3:1 hexanes:EtOAc).

mp: 126–129 °C.

Compound 524

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.97 (t, *J* = 2.8 Hz, 1H, C*H*O), 7.10 (s, 1H, Ar*H*), 3.96 (t, *J* = 8.4 Hz, 2H, N*CH*$_2$CH$_2$), 3.13 (t, *J* = 8.6 Hz, 2H, NCH$_2$*CH*$_2$), 2.83 (s, 3H, O$_2$SC*H*$_3$), 2.76 (d, *J* = 2.9 Hz, 2H, C*H*$_2$CHO), 2.24 (s, 3H, ArC*H*$_3$), 2.12 (s, 3H, ≡CC*H*$_3$), and 1.46 (s, 6H, C(C*H*$_3$)$_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ 201.4, 152.8, 139.5, 129.2, 128.7, 122.2, 108.2, 94.3, 80.1, 75.9, 55.6, 50.5, 34.3, 27.9, 27.2, 15.1, and 4.6.

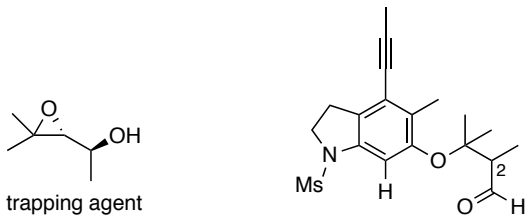
IR (neat): 2986, 2920, 2873, 2852, 2228, 1720, 1593, 1551, 1458, 1421, 1386, 1321, 1161, 1159, 1125, 1096, 1058, and 969 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{18}H_{24}NO_4S^+$ [M+H$^+$] 350.1426, found 350.1416.

TLC: R_f 0.15 (3:1 hexanes:EtOAc).

mp: 84–87 °C.

2,3-Dimethyl-3-((5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)oxy)butanal (527)



Prepared following General Experimental Procedure A. Polyyne substrate: **215** (30.0 mg, 0.121 mmol). Trapping agent: (±)-(*R**)-1-((*S**)-3,3-dimethyloxiran-2-yl)ethanol (42.2 mg, 0.364 mmol). The indoline derivative **527** (10.2 mg) was isolated by MPLC (hexanes:EtOAc 2:1), in 23% yield and as a white amorphous solid. Along with 21.0 g (48%) of indoline derivative **525**.

Compound 527

^{1}H NMR (500 MHz, $CDCl_3$): δ 10.03 (d, *J* = 2.5 Hz, 1H, C*H*O), 7.09 (s, 1H, Ar*H*), 3.97 (t, *J* = 8.5 Hz, 2H, N*CH*$_2$CH$_2$), 3.13 (t, *J* = 8.4 Hz, 2H, NCH$_2$*CH*$_2$), 2.83 (s, 3H, O$_2$SC*H*$_3$), 2.77 (qd, *J* = 7.0, 2.5 Hz, 1H, C2*H*), 2.24 (s, 3H, ArC*H*$_3$), 2.12 (s, 3H, ≡CC*H*$_3$), 1.374 [s, 3H, C(C$_a$*H*$_3$)(C$_b$H$_3$)], 1.369 [s, 3H, C(C$_a$H$_3$)(C$_b$*H*$_3$)], and 1.22 (d, *J* = 7.0 Hz, 3H, C*H*$_3$CH). HSQC and HMBC were also used to make this assignment.

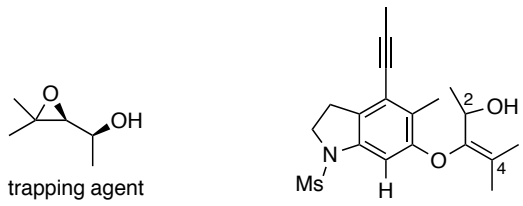
^{13}C NMR (125 MHz, $CDCl_3$): δ 204.5, 152.7, 139.5, 129.2, 128.5, 122.2, 108.3, 94.2, 83.0, 76.0, 56.4, 50.6, 34.3, 27.9, 25.3, 24.0, 15.1, 9.7, and 4.6.

IR (neat): 2980, 2919, 2881, 2853, 2735, 2228, 1720, 1592, 1458, 1345, 1320, 1223, 1157, 1124, 1095, 1058, and 969 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{19}H_{25}NNaO_4S^+$ [M+Na$^+$] 386.1402, found 386.1395.

TLC: R_f 0.1 (2:1 hexanes:EtOAc).

4-Methyl-3-((5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)oxy)pent-3-en-2-ol (529)



Prepared following General Experimental Procedure A. Polyyne substrate: **215** (30.0 mg, 0.121 mmol). Trapping agent: (±)-(*R**)-1-((*R**)-3,3-dimethyloxiran-2-yl)ethan-1-ol (42.2 mg, 0.364 mmol). The indoline derivative **529** (29.7 mg) was isolated by MPLC (hexanes:EtOAc 2:1) in 67% yield as a white amorphous solid.

Compound 529

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.91 (s, 1H, Ar*H*), 4.85 (br q, *J* = 6.3 Hz, 1H, C2*H*), 3.97 (ddd, *J* = 10.5, 8.0, 8.0 Hz, 1H, N*CH*$_a$H$_b$CH$_2$), 3.92 (ddd, *J* = 10.6, 8.4, 8.4 Hz, 1H, N*C*H$_a$*H*$_b$CH$_2$), 3.10 (t, *J* = 8.4 Hz, 2H, NCH$_2$*CH*$_2$), 2.76 (s, 3H, O$_2$SC*H*$_3$), 2.34 (s, 3H, ArC*H*$_3$), 2.13 (s, 3H, ≡CC*H*$_3$), 1.85 [s, 3H, =C(C$_a$*H*$_3$)(C$_b$H$_3$)], 1.69 (br s, 1H, O*H*), 1.52 [s, 3H, =C(C$_a$H$_3$)(C$_b$*H*$_3$)], and 1.27 (d, *J* = 6.6 Hz, 3H, C*H*$_3$CH). HSQC and HMBC were also used to make this assignment.

^{13}C NMR (125 MHz, $CDCl_3$): δ 156.3, 145.4, 139.8, 125.9, 123.1, 122.0, 121.8, 99.9 (*C*7'), 93.8, 75.9, 65.4 (*C2*), 50.7 (N*C*H$_2$), 34.0 (*C*H$_3$S), 27.9 (Ar*C*H$_2$), 21.2 (*C*1), 18.4 [=C(*C*$_a$H$_3$)(C$_b$H$_3$)], 18.2 [=C(C$_a$H$_3$)(*C*$_b$H$_3$)], 13.6 (Ar*C*H$_3$), and 4.5 (≡C*C*H$_3$).

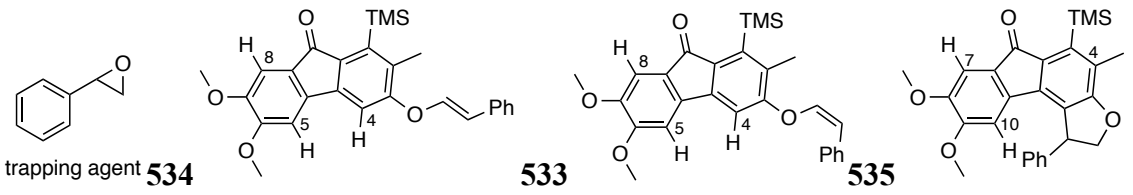
IR (neat): 3431, 2980, 2919, 2858, 2230, 1590, 1453, 1443, 1376, 1343, 1317, 1260, 1155, 1131, 1087, 1057, 995, and 966 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{19}H_{25}NNaO_4S^+$ [M+Na$^+$] 386.1402, found 386.1395.

TLC: R_f 0.1 (2:1 hexanes:EtOAc).

(*E*)-6,7-Dimethoxy-2-methyl-3-(styryloxy)-1-(trimethylsilyl)-9*H*-fluoren-9-one (534), (Z)-6,7-Dimethoxy-2-methyl-3-(styryloxy)-1-(trimethylsilyl)-9H-fluoren-9-one (533), and

8,9-Dimethoxy-4-methyl-1-phenyl-5-(trimethylsilyl)-1,2-dihydro-6*H*-fluoreno[3,4-*b*]furan-6-one (535)



Prepared following General Experimental Procedure A. Polyyne substrate: **226** (30.0 mg, 0.0924 mmol). Trapping agent: 2-phenyloxirane (33.3 mg, 0.277 mmol). In order of elution (hexanes:EtOAc 3:1), the fluorenone derivatives **534** (19.5 mg), **533** (4.8 mg), and **535** (13.5 mg) were isolated in 47%, 12%, and 33% yield. Compound **19** partially coeluted with **535** and was obtained as an ca. 1.5:1 mixture (with **535** as the minor component). Each of **534** and **535** was obtained as a pure substance and was an orange crystalline solid.

This experiment was also carried out on a 1 mmol scale of polyyne substrate **226** (324.5 mg, 1 mmol), and the reaction yielded fluorenone derivatives **534** (231.8 mg), **533** (59.9 mg), and **535** (152.0 mg) in 52%, 13%, and 34% yield, respectively.

Compound 534

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.33 (m, 4H, C_6H_5), 7.28–7.23 (m, 1H, C_6H_5), 7.16 (d, *J* = 12.5 Hz, C=C*H*OAr or C=C*H*Ph), 7.12 (s, 1H, *H8*), 6.99 (s, 1H, *H4 or H5*), 6.91 (s, 1H, *H5 or H4*), 6.41 (d, *J* = 12.5 Hz, 1H, C=C*H*Ph or C=C*H*OAr), 3.99 (s, 3H, C6OC*H*$_3$), 3.91 (s, 3H, C7OC*H*$_3$), 2.36 (s, 3H, ArC*H*$_3$), and 0.44 [s, 9H, Si(C*H*$_3$)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.5, 158.8, 154.2, 149,7, 144.8, 143.9, 143.1, 137.8, 135.2, 134.9, 132.9, 128.8, 127.1, 127.0, 125.8, 114.7, 108.1, 106.8, 102.8, 56.5, 56.2, 16.7, and 2.7.

IR (neat): 3007, 2953, 2902, 2838, 1704, 1654, 1586, 1561, 1555, 1495, 1464, 1445, 1421, 1387, 1354, 1296, 1246, 1174, 1148, 1120, 1078, 1011, and 931 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{27}H_{29}O_4Si^+$ [M+H$^+$] 445.1835, found 445.1824.

TLC: R_f 0.3 (5:1 hexanes:EtOAc).

mp: 178–183 °C.

Compound 533, which partially coeluted with 535, was obtained as an ca. 1.5:1 mixture (with 535 as the minor component)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71-7.68 (d, *J* = 8.0 Hz, 2H, Ph*Ho*), 7.38–7.34 (m, 2H, Ph*Hm*), 7.25 (tt, *J* = 6.8, 1.3 Hz, 1H, PhH_p), 7.13 (s, 1H, *H8*), 7.06 (s, 1H, *H5*), 6.92 (s, 1H, *H4*), 6.61 (d, *J* = 6.9 Hz, 1H, C=C*H*OAr or C=C*H*Ph), 5.76 (d, *J* = 6.9 Hz, 1H, C=C*H*Ph or C=C*H*OAr, 4.00 (s, 3H, C6OCH_3), 3.91 (s, 3H, C7OCH_3), 2.45 (s, 3H, ArCH_3), and 0.45 [s, 9H, Si(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 194.1, 158.9, 154.2, 149,7, 144.9, 143.9, 141.1, 137.7, 135.2, 134.5, 132.8, 128.7, 128.5, 127.7, 127.0, 111.8, 107.9, 106.8, 102.7, 56.4, 56.2, 17.0, and 2.7.

IR (neat): 3005, 2958, 2905, 2832, 1703, 1589, 1573, 1495, 1463, 1439, 1421, 1385, 1366, 1352, 1314, 1217, 1172, 1149, 1093, 1019, and 986 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{27}H_{29}O_4Si^+$ [M+H$^+$] 445.1835, found 445.1825.

TLC: R_f 0.15 (5:1 hexanes:EtOAc).

Compound 535

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.32 (m, 2H, C_6H_5), 7.29–7.26 (m, 3H, C_6H_5), 7.06 (s, 1H, *H7*), 6.13 (s, 1H, *H10*), 5.01 (dd, *J* = 10.0, 8.9 Hz, 1H, OCH_aH$_b$), 4.86 (dd, *J* = 9.9, 6.8 Hz, 1H, OCH$_a$$H_b$), 4.41 (dd, *J* = 8.9, 6.7 Hz, 1H, PhC*H*), 3.83 (s, 3H, C8OCH_3), 3.45 (s, 3H, C9OCH_3), 2.33 (s, 3H, ArCH_3), and 0.44 [s, 9H, Si(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 193.2, 164.3, 153.2, 149,0, 143.3, 142.0, 140.6, 136.7, 134.2, 129.4, 127.9, 127.7, 127.6, 124.1, 123.2, 106.4, 106.3, 79.5, 56.1, 56.0, 47.8, 16.3, and 2.8.

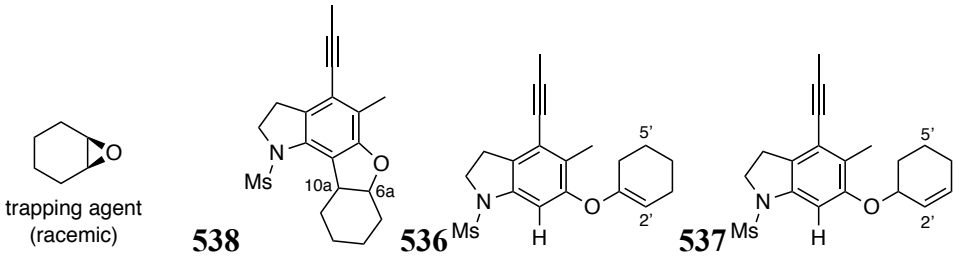
IR (neat): 3006, 2957, 2925, 2843, 1702, 1595, 1505, 1458, 1438, 1360, 1327, 1215, 1159, 1124, 1092, 1034, and 976 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{27}H_{29}O_4Si^+$ [M+H$^+$] 445.1835, found 445.1828.

TLC: R_f 0.1 (5:1 hexanes:EtOAc).

mp: 195–197 °C.

5-Methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)-2,3,6a,7,8,9,10,10a-octahydro-1*H*-benzofuro[2,3-*g*]indole (538),
6-(Cyclohex-1-en-1-yloxy)-5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indoline (536) and
6-(Cyclohex-2-en-1-yloxy)-5-methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indoline (537)



Prepared following General Experimental Procedure A. Polyyne substrate: **215** (30.0 mg, 0.121 mmol). Trapping agent: cyclohexene oxide (35.7 mg, 0.364 mmol). In order of elution (hexanes:EtOAc 6:1), the indoline derivatives **538** (11.4 mg, 27% yield) and a coeluting mixture of **536** and **537** (25.2 mg, 60% yield) were isolated. The two alkene isomers were present in an ca. 1:4 ratio (^{1}H NMR analysis). Each sample was a white amorphous solid.

Data for Compound 538

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.58 (ddd, *J* = 6.7, 3.9, 3.3 Hz, 1H, OC*H*), 4.15 (ddd, *J* = 12.4, 9.0, 3.5 Hz, 1H, N$CH_aH_bCH_2$), 3.96 (ddd, *J* = 12.4, 10.3, 9.2 Hz, 1H, $NCH_aH_bCH_2$), 3.68 (ddd, *J* = 10.4, 6.5, 6.5 Hz, 1H, OCHC*H*Ar), 3.13 (ddd, *J* = 15.9, 9.7, 9.3 Hz, 1H, $NCH_2CH_aH_b$), 2.94 (ddd, *J* = 15.9, 9.1, 3.4 Hz, 1H, $NCH_2CH_aH_b$), 2.79 (s, 3H, O_2SCH_3), 2.25 (s, 3H, $ArCH_3$), 2.18 (ddddd, *J* = 15.0, 3.8, 3.8, 3.8, 1.5 Hz, 1H, $H7_{eq}$), 2.11 (s, 3H, $\equiv CCH_3$), 2.09–2.02 (nfom, 1H), 1.74 (dddd, *J* = 14.8, 12.0, 4.6, 4.6 Hz, 1H, $H7_{ax}$), 1.59–1.52 (m, 2H), 1.52–1.42 (nfom, 1H), 1.30–1.19 (nfom, 1H), and 1.11 (dddd, *J* = 13.5, 12.3, 10.3, 3.3 Hz, 1H, $H10_{ax}$). HSQC and HMBC were also used to make this assignment.

^{13}C NMR (125 MHz, $CDCl_3$): δ 158.7, 134.9, 129.1, 124.4, 120.1, 119.1, 93.0, 82.4, 76.1, 52.5, 40.8, 35.5, 28.8, 27.5, 27.3, 22.6, 20.3, 13.4, and 4.5.

IR (neat): 3000, 2920, 2867, 2226, 1617, 1590, 1450, 1419, 1404, 1381, 1349, 1309, 1297, 1272, 1239, 1214, 1186, 1160, 1133, 1106, 1084, 1050, 1022, 993, and 967 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{19}H_{24}NO_3S^+$ $[M+H^+]$ 346.1478, found 346.1469.

TLC: R_f 0.2 (6:1 hexanes:EtOAc).

Data for compound 536 (enol ether)

^{1}H NMR [500 MHz, $CDCl_3$, deduced from the mixture of **536** and **537**]: δ 7.01 (s, 1H, Ar*H*), 4.59 (tt, *J* = 3.9, 1.3 Hz, 1H, C2'*H*), 3.97 (m, overlapped with analogous resonance for **537**, 2H, N*CH*$_2$), 3.14 (t, *J* = 8.6 Hz, 2H, Ar*CH*$_2$), 2.82 (s, overlapped with analogous resonance for **537**, 3H, O_2SCH_3), 2.21–2.17 (m, 2H, C_aH_2), 2.20 (s, 3H, Ar*CH*$_3$), 2.12 (s, 3H, ≡C*CH*$_3$), 2.01–1.97 (m, 2H, C_bH_2), 1.74 (nfom, Σ*J*s = 24 Hz, 2H, C_cH_2), and 1.56 (nfom, Σ*J*s = 24 Hz, 2H, C_dH_2). HSQC and HMBC were also used to make this assignment.

^{13}C NMR (125 MHz, $CDCl_3$, deduced from the mixture of **536** and **537**): δ 153.2, 139.9, 132.2, 128.9, 127.4, 126.5, 106.7, 102.3, 93.6, 75.8, 50.6, 34.1, 27.9, 26.8, 23.4, 22.8, 22.3, 13.6, and 4.5.

IR (neat of the mixture of **536** and **537**): 3026, 2929, 2861, 2234, 1589, 1456, 1338, 1321, 1305, 1268, 1189, 1152, 1098, 1061, 1025, 1000, and 966 cm^{-1}.

HRMS (ESI-TOF of the mixture of **536** and **537**): Calculated for $C_{19}H_{24}NO_3S^+$ [M+H$^+$] 346.1478, found 346.1467.

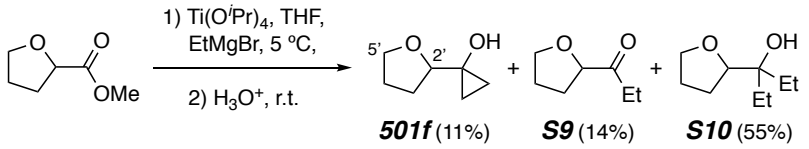
TLC: R_f 0.1 (6:1 hexanes:EtOAc).

Data for compound 537 (allylic ether)

^{1}H NMR [500 MHz, $CDCl_3$, deduced from the mixture of **536** and **537**]: δ 7.02 (s, 1H, Ar*H*), 5.94 (dddd, *J* = 10.1, 3.7, 3.7, 1.2 Hz, 1H, *H2'*), 5.83 (dddd, *J* = 10.1, 3.4, 2.2, 2.2 Hz, 1H, *H3'*), 4.72 (m, Σ*J*s = 19 Hz, 1H, C*H*OAr), 3.96 (m, overlapped with analogous resonance for **536**, 2H, N*CH*$_2$), 3.12 (t, *J* = 8.6 Hz, 2H, Ar*CH*$_2$), 2.82 (s, overlapped with analogous resonance for **536**, 3H, O_2SCH_3), 2.25 (s, 3H, Ar*CH*$_3$), 2.17–2.08 (m, 1H, $C_aH_aH_b$), 2.11 (s, 3H, ≡C*CH*$_3$), 2.05–1.99 (m, 1H, $C_aH_aH_b$), 1.93–1.80 (m, 3H, C_bH_2 and $C_cH_aH_b$), and 1.68–1.60 (m, 1H, $C_cH_aH_b$). HSQC and HMBC were also used to make this assignment.

^{13}C NMR (125 MHz, $CDCl_3$, deduced from the mixture of **536** and **537**): δ 155.9, 139.8, 132.2, 126.2, 125.7, 125.6, 121.9, 101.0, 93.6, 76.1, 72.2, 50.7, 34.1, 28.5, 27.9, 25.1, 19.0, 13.9, and 4.5.

1-(Tetrahydrofuran-2-yl)cyclopropan-1-ol (501f)



To a stirred solution of freshly distilled Ti(O^{i}Pr)$_4$ (85 mg, 90 μL, 0.3 mmol) and methyl tetrahydrofuroate (130 mg, 1 mmol) in dry THF (0.5 mL) was added a solution of EtMgBr (4.4 mL, 0.688 M in THF, 3 mmol) by syringe pump over 3 hours. The reaction mixture was maintained under 15 ºC and allowed to warm to ambient temperature after the addition. The mixture was then quenched with saturated NH_4Cl solution and filtered through Celite. The mixture was extracted with ether (8 mL X 3), washed with brine, and dried over $MgSO_4$. The combined organic layer was then concentrated and purified by MPLC. Initial elution with a 3:1 mixture of hexanes:EtOAc 3:1 provided a coeluting mixture of the known ketone **S9**[138] and the known tertiary alcohol **S10**,[139] respectively.[140] Further elution with 100% ethyl acetate provide the cyclopropanol **501f** (corrected for EtOAc: 14.3 mg, 11% yield). This sample contains ca. 32 wt% of ethyl acetate (^{1}H NMR integration), which was deemed acceptable for use in the subsequent trapping experiment.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.95 (nfom, Σ*J* = 21 Hz, 1H, *H5'a*), 3.87 (nfom, Σ*J* = 21 Hz, 1H, *H5'b*), 3.51 (nfom, Σ*J* = 14 Hz, 1H, *H2'*), 2.75 (s, 1H, O*H*), 2.03–1.82 (m, 4H, *H3'* and *H4'*), 0.83 (ddd, *J* = 10.5, 5.5, 3.8 Hz, 1H, *H2* or *H3*), 0.80 (ddd, *J* = 10.6, 5.5, 4.4 Hz, 1H, *H2* or *H3*), 0.59 (nfom, 1H, *H2* or *H3*), and 0.52 (nfom, 1H, *H3* or *H2*). HSQC was used to guide the assignment of protons.

^{13}C NMR (125 MHz, $CDCl_3$): 84.2, 68.9, 56.2, 27.3, 26.3, 13.1, and 9.8.

IR (neat): 3400, 2974, 2954, 2873, 1459, 1415, 1376, 1356, 1299, 1231, 1181, 1063, 1011, and 968 cm^{-1}.

TLC: R_f 0.1 (2:1 hexanes:EtOAc).

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[138] Baettig, U.; D'Souza, A.; Hunt, P.; Press, N. J.; Watson, S. J. Organic Chemistry. U.S. Pat. Appl. 20100029670, 2010.

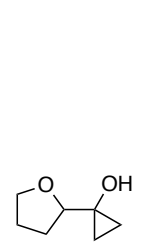
[139] van Tamelen, E. E.; Schwartz, J.; Brauman, J. I. Ketone Enolate Photochemistry. *J. Am. Chem. Soc*. **1970**, *92*, 5798–5799.

[140] For some substrates the Kulinkovich reaction is reported to give competing product formation arising from diethyl addition product as the major product, see Racouchot, S.; Ollivier, J.; Salaün, J. Titanium-Mediated Diastereoselective Formation of (Z)-1-(1-Alkenyl)-2- substituted-cyclopropyl Esters Efficient Precursors of (Z)- 2,3-Methanoamino Acids. *Synlett* **2000**, 1729–1732.

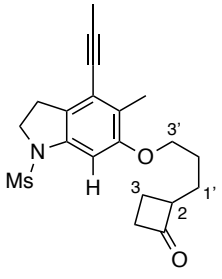
GC-MS (EI, 70 eV): t_R = 3.22 min. Calculated for $C_7H_{12}O_2^+$ [M^+] 128, found: *m/z* (%) 128 (3, M^+), 100 (15, M^+ - CH_2=CH_2), 71 (100, $C_4H_7O^+$), and 57 (15, $C_3H_5O^+$).

HRMS (ESI-TOF): Calculated for $C_7H_{12}NaO_2^+$ [M+Na^+] 151.0735, found 151.0751.

2-(3-((5-Methyl-1-(methylsulfonyl)-4-(prop-1-yn-1-yl)indolin-6-yl)oxy)propyl)cyclobutan-1-one (521)



trapping agent **501f**



521

Prepared following General Experimental Procedure A. Polyyne substrate: **215** (10.0 mg, 0.0404 mmol). Trapping agent: 1-(tetrahydrofuran-2-yl)cyclopropan-1-ol (14.3 mg, 0.112 mmol). The indoline derivative **521** (11.9 mg) was isolated by MPLC (hexanes:EtOAc 2:1) in 79% yield as a white crystalline solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.92 (s, 1H, Ar*H*), 3.96 (t, *J* = 8.5 Hz, 2H, N*CH*$_2$CH$_2$), 3.94 (t, *J* = 5.6 Hz, 2H, C3'*H*$_2$), 3.35 (dddddd, *J* = 10.3, 8.3, 7.4, 6.3, 2.7, 2.7 Hz, 1H, C2*H*), 3.11 (t, *J* = 8.7 Hz, 2H, NCH$_2$C*H*$_2$), 3.03 (dddd, *J* = 17.8, 10.6, 7.8, 2.7 Hz, 1H, C4*H*$_a$H$_b$), 2.94 (dddd, *J* = 17.6, 9.6, 5.4, 2.8 Hz, 1H, C4H$_a$*H*$_b$), 2.82 (s, 3H, O$_2$SC*H*$_3$), 2.24 (s, 3H, ArC*H*$_3$), 2.23 (dddd, *J* = 11.0, 10.3, 10.3, 5.2 Hz, 1H, C3*H*$_a$H$_b$), 2.12 (s, 3H, ≡CC*H*$_3$), 1.95–1.81 (m, 3H, C2'*H*$_2$ and C1'*H*$_a$H$_b$), 1.74–1.67 (m, 1H, C1'H$_a$*H*$_b$), and 1.68 (dddd, *J* = 11.1, 9.8, 7.7, 7.7 Hz, 1H, C3H$_a$*H*$_b$). HSQC and HMBC were used to guide this assignment.

^{13}C NMR (125 MHz, $CDCl_3$): δ 211.7, 156.8, 139.8, 125.1, 124.3, 121.7, 98.5, 93.6, 76.0, 68.2 (C3'), 60.0 (C2), 50.7, 44.5 (C4), 34.1, 27.8, 26.9 (C2'), 26.3 (C1'), 17.0 (C3), 13.6, and 4.5.

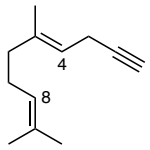
IR (neat): 2923, 2872, 2230, 1775, 1592, 1457, 1395, 1347, 1314, 1238, 1211, 1150, 1146, 1096, 1059, and 968 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{20}H_{25}NNaO_4S^+$ [M+Na^+] 398.1402, found 398.1386.

TLC: R_f 0.2 (2:1 hexanes:EtOAc).
mp: 134–136 °C.

Supplementary Information for Chapter 6

(*E*)-5,9-Dimethyldeca-4,8-dien-1-yne (S10)



To a stirred culture tube containing neat geranyl bromide (**612**, 1.09 g, 5.0 mmol) was added a solution of ethynyl magnesium bromide (0.5 M in THF, 15 mL, 7.5 mmol). The reaction mixture was heated overnight in a screw-capped culture tube in an oil bath held at ca. 60 °C. The solution was then quenched with sat. NH_4Cl solution, extracted with hexanes (3X, 10 mL each), and washed with brine. The combined organic layer was dried and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc 11:1) to give dienyne **S10** as a yellow oil (772 mg, 95%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.21 (ttq, *J* = 6.9, 1.4, 1.4 Hz, 1H, C4*H*), 5.09 (tqq, *J* = 6.9, 1.3, 1.3 Hz, 1H, C8*H*), 2.90 (ddtq, *J* = 6.9, 2.7, 0.8, 0.8 Hz, 2H, C≡CC*H*$_2$CH=C), 2.08 (br dt, *J* = 7, 7 Hz, 2H, C7*H*$_2$), 2.01 (br t, *J* = 7 Hz, 2H, C6*H*$_2$), 1.97 (t, *J* = 2.8 Hz, 1H, C≡C*H*), 1.68 (br d, *J* = 1.2 Hz, 3H, C9EC*H*$_3$), 1.63 (br d, *J* = 1.0 Hz, 3H, C5C*H*$_3$), and 1.60 (br d, *J* = 1.1 Hz, 3H, C9ZC*H*$_3$).

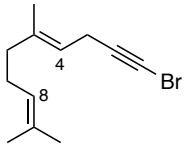
^{13}C NMR (125 MHz, $CDCl_3$): δ 137.9, 131.7, 124.0, 118.2, 83.5, 67.6, 39.4, 26.5, 25.7, 17.7, 17.5, and 16.1.

IR (neat): 3308, 2968, 2917, 2856, 2729, 1446, 1377, 1285, 1232, 1109, 1081, and 985 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{12}H_{19}^+$ [M+H$^+$] 163.1481, found 163.1479.

TLC: R_f 0.3 (100% hexanes).

(*E*)-1-Bromo-5,9-dimethyldeca-4,8-dien-1-yne (610)



To a stirred solution of dienyne **S10** (649 mg, 4.0 mmol) in 5 mL of THF was added a solution of *n*-BuLi (2.5 M in hexanes, 1.68 mL, 4.2 mmol) dropwise at -78 ºC. The resulting lithium acetylide solution was stirred for an additional 10 min, followed by the dropwise addition of a solution of NBS (854 mg, 4.8 mmol) in THF (8 mL) at -78 ºC. The reaction mixture was allowed to warm to ambient temperature and further stirred for 2 h. The light yellow slurry was quenched with sat. NH_4Cl solution, extracted with hexanes (3X, 10 mL each), and washed with brine. The combined organic layer was dried and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc 11:1) to give the bromoalkyne **610** as an orange oil (963 mg, 99%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.17 (ttq, *J* = 6.8, 1.4, 1.4 Hz, 1H, C4*H*), 5.08 (tqq, *J* = 6.8, 1.3, 1.3 Hz, 1H, C8*H*), 2.91 (dtq, *J* = 6.9, 0.8, 0.8 Hz, 2H, C≡CC*H*$_2$CH=C), 2.07 (br dt, *J* = 7, 7 Hz, 2H, C7*H*$_2$), 2.00 (br t, *J* = 7 Hz, 2H, C6*H*$_2$), 1.68 (dt, *J* = 1.3, 1.3 Hz, 3H, C9EC*H*$_3$), 1.62 (dt, *J* = 1.4, 0.9 Hz, 3H, C5C*H*$_3$), and 1.60 (br d, *J* = 1.0 Hz, 3H, C9ZC*H*$_3$).

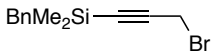
^{13}C NMR (125 MHz, $CDCl_3$): δ 138.0, 131.7, 123.9, 117.7, 79.1, 39.4, 26.4, 25.7, 18.7, 17.7, and 16.1. (bromine-bearing alkyne carbon not identified)

IR (neat): 2968, 2927, 2855, 2728, 1445, 1377, 1327, 1286, 1226, 1204, 1152, 1086, and 985 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{12}H_{18}{}^{79}Br^+$ [M+H$^+$] 241.0586, found 241.0585.

TLC: R_f 0.3 (100% hexanes).

Benzyl(3-bromoprop-1-yn-1-yl)dimethylsilane (609b)

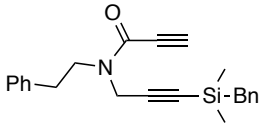


To a stirred solution of propargyl bromide (80 wt% in toluene, 781 mg, 0.6 mL, 5.25 mmol) in THF (7 mL) was added a solution of *n*-BuLi (2.5 M in hexanes, 2.0 mL, 5.0 mmol) dropwise at -78 ºC. The reaction mixture was stirred at -78 ºC for 30 min, followed by the addition of benzyldimethylsilyl chloride (970 mg, 953 μL, 5.25 mmol) in THF (1 mL). The reaction mixture was kept at -78 ºC for an additional 30 min, allowed to warm to 0 ºC, and stirred for an additional 2 h. The light yellow reaction mixture was quenched by the addition of saturated NH_4Cl solution (10 mL), and the aqueous layer was extracted three times with hexanes (10 mL each). The combined organic layer was washed with brine (10 mL), dried with $MgSO_4$, filtered, and concentrated. The resulting residue was purified by flash column chromatography (100% hexanes) to give silane **609b** as a colorless oil (888 mg, 66%). This sample contained ca. 30% of two additional, coeluting (non-polar) impurities. Therefore, the corrected yield of **609b** is ca. 46%.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (br t, *J* = 7.7 Hz, 2H, PhH_m), 7.10 (br t, *J* = 7.7 Hz, 1H, PhH_p), 7.08 (br d, *J* = 7.7 Hz, 2H PhH_m), 3.90 (s, 2H, C≡CCH_2Br), 2.21 (s, 2H, PhCH_2), and 0.13 [s, 6H, Si(CH_3)$_2$].

TLC: R_f 0.2 (100% hexanes).

***N*-(3-(Benzyldimethylsilyl)prop-2-yn-1-yl)-*N*-phenethylpropiolamide (623b)**



To a stirred slurry of NaH (60 wt% in mineral oil, 6.9 mg, 0.289 mmol) in THF (0.5 mL) was added a solution of amide ## (50.0 mg, 0.289 mmol) in THF (0.5 mL) dropwise at 0 ºC. The reaction mixture was stirred at 0 ºC for 30 min, followed by the addition of propargyl bromide **609b** (300 mg, 1.12 mmol) in THF (0.5 mL). The reaction mixture was allowed to warm to ambient temperature and stirred for an additional 2 h. The reaction mixture was quenched by the addition of saturated NH_4Cl solution (5 mL), and the aqueous layer was extracted three times with ethyl acetate (5 mL each). The combined organic layer was washed with brine (10 mL), dried with $MgSO_4$, filtered, and concentrated. The resulting residue was purified by MPLC (6:1 hexanes:EtOAc) to give diyne **623b** as a colorless oil (32.6 mg, 31%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33–7.28 (m, 2H, PhH), 7.27–7.16 (m, 5H, PhH), 7.10–7.03 (m, 3H, PhH), 4.26 (s, 0.8H, C≡CCH_2N, minor), 4.25 (s, 1.2H, C≡CCH_2N, major), 3.87 (nfot, J = 7.8 Hz, 1.2H, NCH_2CH$_2$, major), 3.68 (nfot, J = 7.8 Hz, 0.8H, NCH_2CH$_2$, minor), 3.13 (s, 0.4H, C≡CH, minor), 3.09 (s, 0.6H, C≡CH, major), 2.94 (nfot, J = 7.9 Hz, 1.2H, NCH$_2$CH_2, major), 2.89 (nfot, J = 7.6 Hz, 0.8H, NCH$_2$CH_2, minor), 2.20 (s, 1.2H, PhCH_2, major), 2.19 (s, 0.8H, PhCH_2, minor), 0.142 [s, 2.4H, Si(CH_3)$_2$, minor], and 0.140 [s, 3.6H, Si(CH_3)$_2$, major]. (Amide rotamer ratio major:minor = 3:2)

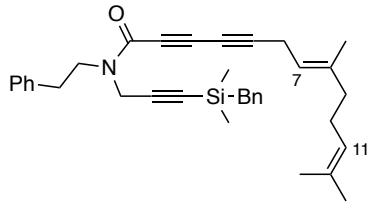
^{13}C NMR (125 MHz, $CDCl_3$): δ 152.88 (maj), 152.75 (min), 138.7 (maj), 138.6 (min), 138.5 (min), 137.8 (maj), 128.78 (maj), 128.77 (min), 128.7 (maj), 128.6 (min), 128.32 (maj), 128.30 (min), 128.24 (min), 128.22 (maj), 126.8 (maj), 126.6 (min), 124.52 (min), 124.47 (maj), 100.59 (maj), 100.51 (min), 88.8 (min), 88.3 (maj), 79.2 (min), 78.8 (maj), 75.5 (maj), 75.4 (min), 49.7 (maj), 46.4 (min), 40.2 (min), 35.1 (maj), 34.7 (maj), 33.4 (min), 26.01 (maj), 25.96 (min), -2.21 (maj), and -2.23 (min). (Amide rotamer ratio major:minor = 3:2)

IR (neat): 3269, 3220, 3082, 3061, 3026, 2959, 2929, 2896, 2179, 2105, 1633, 1600, 1493, 1453, 1415, 1367, 1341, 1250, 1231, 1206, 1155, 1083, 1057, 1015, and 977 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{23}H_{26}NOSi^+$ [M+H$^+$] 360.1778, found 360.1771.

TLC: R_f 0.2 (6:1 hexanes:EtOAc).

(*E*)-*N*-(3-(Benzyldimethylsilyl)prop-2-yn-1-yl)-8,12-dimethyl-*N*-phenethyltrideca-7,11-dien-2,4-diynamide (608b)



Cuprous chloride (4.4 mg, 0.0445 mmol) and hydroxylamine hydrochloride (12.4 mg, 0.178 mmol) were added to a 2-dram vial equipped with a magnetic stirrer bar. The reaction vessel was purged with nitrogen and then a solution of 40% *n*-$BuNH_2$/H_2O (0.3 mL) and DCM (0.2 mL) were added. The colorless mixture was cooled to 0 ºC. In the meantime, a solution of diyne **623b** (32.0 mg, 0.089 mmol) in DCM (0.6 mL) was prepared, and the diyne solution was added in a dropwise fashion into the reaction vial under N_2. The reaction was stirred at 0 ºC for 5 min, and a solution of bromoalkyne **610** (42.9 mg, 0.178 mmol) in DCM (0.6 mL) was added slowly (1 drop per 2 seconds). After the addition, the reaction mixture was allowed to warm to ambient temperature and the progress was monitored by TLC. The reaction mixture turned dark green while stirring. An additional 12.4 mg of hydroxylamine hydrochloride was added, and the reaction mixture turn back to orange. The reaction mixture was then quenched by the addition of saturated NH_4Cl solution (5 mL), and the aqueous layer was extracted three times with DCM (5 mL each). The combined organic layer was washed with saturated NH_4Cl solution (5 mL) and brine (5 mL), dried with $MgSO_4$, filtered, and concentrated. The resulting residue was purified by MPLC (15:1 hexanes:EtOAc) to give amide **608b** as a colorless oil (28.0 mg, 61%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34–7.27 (m, 2H, PhH), 7.26–7.16 (m, 5H, PhH), 7.09–7.02 (m, 3H, PhH), 5.20–5.14 (m, 1H, C7*H*, maj+min), 5.11–5.05 (m, 1H, C11*H*, maj+min), 4.22 (s, 1.2H, C≡CCH_2N, major), 4.21 (s, 0.8H, C≡CCH_2N, minor), 3.83 (nfot, *J* = 7.6 Hz, 1.2H, NC$H_2$$CH_2$, major), 3.67 (nfot, *J* = 7.8 Hz, 0.8H, NC$H_2$$CH_2$, minor), 3.08 (br d, *J* = 6.8 Hz, 1.2H, C≡CCH_2C=C, major), 3.06 (br d, *J* = 6.9 Hz, 0.8H, C≡CCH_2C=C, minor), 2.92 (nfot, *J* = 7.7 Hz, 1.2H, NCH_2CH_2, major), 2.87 (nfot, *J* = 7.7 Hz, 0.8H, NCH_2CH_2, minor), 2.192 (s, 0.8H, PhCH_2, minor), 2.189 (s, 1.2H, PhCH_2, major), 2.13–2.06 (m, 2H, overlapping C10H_2, maj+min), 2.06–1.99 (m, 2H, overlapping C9H_2, maj+min), 1.69 (br s, 3H, overlapping C12ECH_3, maj+min), 1.66 (dt, *J* = 1.3, 0.7 Hz, 1.8H, C8CH_3, major), 1.64 (dt, *J* = 1.3, 0.7 Hz, 1.2H, C8CH_3, minor), 1.61 (br s, 3H,

overlapping C12ZCH_3, maj+min), 0.14 [s, 2.4H, Si(CH_3)$_2$, minor], and 0.13 [s, 3.6H, Si(CH_3)$_2$, major]. (Amide rotamer ratio major:minor = 3:2)

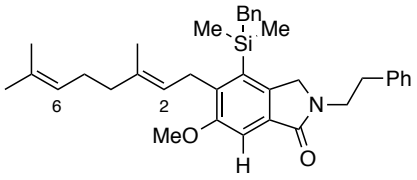
^{13}C NMR (125 MHz, $CDCl_3$): δ 153.1 (maj), 153.0 (min), 139.60 (min), 139.58 (maj), 138.7 (maj), 138.57 (min), 138.54 (min), 137.9 (maj), 131.88 (maj), 131.87 (min), 128.85 (maj), 128.78 (min), 128.72 (maj), 128.6 (min), 128.32 (maj), 128.30 (min), 128.25 (min), 128.22 (maj), 126.8 (maj), 126.5 (min), 124.50 (min), 124.47 (maj), 123.78 (maj+min), 115.8 (maj), 115.7 (min), 100.7 (maj), 100.6 (min), 88.8 (min), 88.2 (maj), 86.65 (min), 86.60 (min), 76.4 (min), 76.0 (maj), 66.2 (maj), 66.1 (min), 63.33 (maj), 63.27 (min), 49.7 (maj), 46.4 (min), 40.1 (min), 39.38 (maj), 39.37 (min), 35.3 (maj), 34.8 (maj), 33.4 (min), 26.40 (maj), 26.37 (min), 26.02 (maj), 25.98 (min), 25.7 (maj+min), 18.63 (maj), 18.61 (min), 17.7 (maj+min), 16.29 (maj), 16.28 (min), -2.20 (maj), and -2.23 (min). (Amide rotamer ratio major:minor = 3:2)

IR (neat): 2963, 2941, 2928, 2890, 2862, 2238, 1637, 1549, 1494, 1453, 1416, 1366, 1342, 1320, 1309, 1252, 1208, 1185, 1154, 1108, 1056, 1019, and 968 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{35}H_{42}NOSi^+$ $[M+H^+]$ 520.3030, found 520.3017.

TLC: R_f 0.2 (15:1 hexanes:EtOAc).

(*E*)-4-(benzyldimethylsilyl)-5-(3,7-dimethylocta-2,6-dien-1-yl)-6-methoxy-2-phenethylisoindolin-1-one (625b)



A solution of polyyne substrate **608b** (28.0 mg, 0.054 mmol) in 2 mL of methanol was heated in a screw-capped culture tube in an oil bath held at ca. 105 °C. After 18 h, the slightly yellow-colored solution was allowed to cool to ambient temperature and concentrated. The resulting residue was purified by MPLC (hexanes:EtOAc 1:1) to give the isoindolinone derivative **625b** as a colorless oil (21.2 mg, 71%). The location of the methoxy group in the product was established by difference NOE experiments.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (s, 1H, Ar*H*), 7.28 (br t, *J* = 8 Hz, 2H, PhH_m), 7.21 (br d, *J* = 7 Hz, 2H, PhH_o), 7.20 (tt, *J* = 6.5, 1.4 Hz, PhH_p), 7.12 (br dd, *J* = 7.4, 7.4 Hz, 2H, PhH_m'), 7.04 (tt, *J* = 6.7, 1.3 Hz,1H, PhH_p'), 6.80 (br d, *J* 7.4 Hz, 2H, PhH_o'), 5.05 (tqq, *J* = 6.6, 1.3, 1.3 Hz, 1H, C6*H*), 4.96 (ttq, *J* = 5.9, 1.3, 1.3 Hz, 1H, C2*H*), 3.87 (s, 3H, OCH_3), 3.78 (br t, *J* = 7.5 Hz, 2H, NCH_2CH$_2$), 3.75 (s, 2H, ArCH_2N), 3.52 (d, *J* = 5.9 Hz, 2H, ArCH_2CH=C), 2.89 (t, *J* = 7.4 Hz, 2H, NCH$_2$CH_2), 2.30 (s, 2H, PhCH_2), 2.04 (br dt, *J* = 7, 7 Hz, 2H, C5H_2), 1.99 (br t, *J* = 7.5 Hz, 2H, C4H_2), 1.74 (dt, *J* = 1.2 Hz, 3H, C7ECH_3), 1.61 (dt, *J* = 1.1, 1.1 Hz, 3H, C7ZCH_3), 1.55 (br s, 3H, C3CH_3), and 0.28 [s, 6H, Si(CH_3)$_2$].

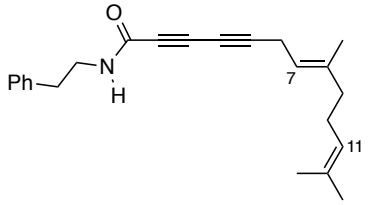
^{13}C NMR (125 MHz, $CDCl_3$): δ 168.4, 158.1, 141.1, 139.4, 139.2, 139.0, 135.3, 132.0, 131.30, 131.29, 128.7, 128.6, 128.3, 128.1, 126.5, 124.4, 124.2, 123.6, 105.9, 55.7, 52.7, 43.9, 39.6, 35.1, 30.3, 27.0, 26.6, 25.7, 17.7, 16.5, and 0.7.

IR (neat): 3080, 3060, 3025, 2962, 2914, 2856, 1681, 1599, 1493, 1469, 1453, 1421, 1401, 1381, 1315, 1272, 1252, 1228, 1202, 1155, 1104, 1077, 1056, 1030, 934, and 908 cm^{-1}.

HRMS (ESI-TOF): Calculated for $C_{36}H_{46}NO_2Si^+$ [M+H$^+$] 552.3292, found 552.3284.

TLC: R_f 0.2 (1:1 hexanes:EtOAc).

(*E*)-8,12-Dimethyl-*N*-phenethyltrideca-7,11-dien-2,4-diynamide (624)



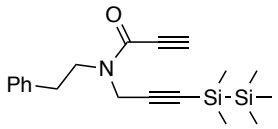
Cuprous chloride (9.9 mg, 0.10 mmol) and hydroxylamine hydrochloride (69.5 mg, 1.0 mmol) were added to a 2-dram vial equipped with a magnetic stirrer bar. The reaction vessel was purged with nitrogen, and a solution of 40% *n*-$BuNH_2$/H_2O (0.5 mL) and DCM (0.5 mL) were added. The colorless mixture was cooled to 0 ºC. In the meantime, a solution of amide **611** (173 mg, 1.0 mmol) in DCM (1.5 mL) was prepared and added in a dropwise fashion into the reaction vial under N_2. This mixture was stirred at 0 ºC for 5 min, and a solution of bromoalkyne **610** (337 mg, 1.4 mmol) in DCM (3 mL) was added slowly (1 drop per 2 seconds). After addition, the reaction mixture was allowed to warm to ambient temperature and the progress was monitored by TLC. The reaction mixture turned dark green; an additional 69.5 mg of hydroxylamine hydrochloride was added and the reaction mixture turn back to orange. The reaction mixture was then quenched by the addition of saturated NH_4Cl solution (10 mL), and the aqueous layer was extracted three times with DCM (5 mL each). The combined organic layer was washed once with saturated NH_4Cl solution (5 mL) and brine (5 mL), dried with $MgSO_4$, filtered, and concentrated. The resulting residue was purified by MPLC (6:1 hexanes:EtOAc) to give amide **624** as an orange oil (160 mg, 48%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (br t, *J* = 7.3 Hz, 2H, PhH_m), 7.25 (tt, *J* = 6.6, 1.3 Hz, 1H, PhH_p), 7.19 (br d, *J* = 7.6 Hz, 2H, PhH_o), 5.77 (br t, *J* = 5 Hz, 1H, N*H*), 5.16 (ttq, *J* = 6.8, 1.3, 1.3 Hz, 1H, C7*H*), 5.08 (tqq, *J* = 6.9, 1.4, 1.4 Hz, 1H, C11*H*), 3.56 (td, *J* = 6.9, 6.2 Hz, 2H, NC$H_2$$CH_2$), 3.02 (dq, *J* = 6.9, 0.9 Hz, 2H, C≡CCH_2C=C), 2.83 (t, *J* = 6.9 Hz, 2H, NCH_2CH_2), 2.07 (br dt, *J* = 7.3, 7.3 Hz, 2H, C10H_2), 2.00 (br d, *J* = 7.7 Hz, 2H, C9H_2), 1.68 (dt, *J* = 1.0, 1.0 Hz, 3H, C12ECH_3), 1.62 (dt, *J* = 0.9, 0.9 Hz, 3H, C12ZCH_3), and 1.61 (br s, 3H, C8CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ 152.2, 139.5, 138.2, 131.9, 128.78, 128.73, 126.7, 123.7, 115.7, 85.0, 70.3, 68.2, 63.1, 41.0, 39.3, 35.3, 26.4, 25.7, 18.5, 17.7, and 16.2.

TLC: R_f 0.1 (6:1 hexanes:EtOAc).

***N*-(3-(1,1,2,2,2-Pentamethyldisilaneyl)prop-2-yn-1-yl)-*N*-phenethylpropiolamide (623a)**



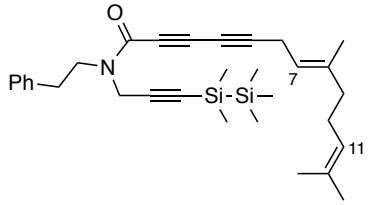
To a stirred slurry of NaH (60 wt% in mineral oil, 13.9 mg, 1.2 mmol) in THF (0.5 mL) was added a solution of amide **611** (50.0 mg, 0.289 mmol) in THF (0.5 mL) dropwise at 0 ºC. The reaction mixture was stirred at 0 ºC for 30 min, followed by the addition of propargyl bromide **609a** (432 mg, 1.73 mmol) in THF (0.5 mL). The reaction mixture was allowed to warm to ambient temperature and further stirred for 2 h. The mixture was then quenched by the addition of saturated NH_4Cl solution (5 mL), and the aqueous layer was extracted three times with ethyl acetate (5 mL each). The combined organic layer was washed with brine (5 mL), dried with $MgSO_4$, filtered, and concentrated. The resulting residue was purified by MPLC (6:1 hexanes:EtOAc) to give diyne **623a** as a colorless oil (17.0 mg, 17%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (br dd, *J* = 7.3, 7.3 Hz, 0.8H, PhH_m, minor), 7.30 (br dd, *J* = 7, 7 Hz, 1.2H, PhH_m, major), 7.27–7.16 (m, 3H, PhH_o and PhH_p), 4.28 (s, 2H, C≡CCH_2N, maj+min), 3.93 (nfot, *J* = 7.5 Hz, 1.2H, NCH_2CH$_2$, major), 3.72 (nfot, *J* = 7.5 Hz, 0.8H, NCH_2CH$_2$, minor), 3.12 (s, 0.4H, C≡C*H*, minor), 3.08 (s, 0.6H, C≡C*H*, major), 2.98 (nfot, *J* = 8.0 Hz, 1.2H, NCH$_2$CH_2, major), 2.92 (nfot, *J* = 8.0 Hz, 0.8H, NCH$_2$CH_2, minor), 0.20 [s, 3.6H, Si(CH_3)$_2$, major], 0.19 [s, 2.4H, Si(CH_3)$_2$, minor], and 0.11 [s, 9H, Si(CH_3)$_2$, maj+min]. (Amide rotamer ratio major:minor = 3:2)

^{13}C NMR (125 MHz, $CDCl_3$): δ 152.85 (maj), 152.79 (min), 138.5 (maj), 137.9 (min), 128.79 (maj), 128.77 (min), 128.72 (maj), 128.6 (min), 126.8 (maj), 126.6 (min), 101.07 (maj), 101.05 (min), 89.4 (min), 89.0 (maj), 79.2 (min), 78.7 (maj), 75.54 (maj), 75.47 (min), 49.6 (maj), 46.4 (min), 40.4 (min), 35.2 (maj), 34.9 (maj), 33.4 (min), -2.58 (maj). -2.60 (min), -3.15 (maj), and -3.23 (min). (Amide rotamer ratio major:minor = 3:2)

TLC: R_f 0.2 (6:1 hexanes:EtOAc).

(*E*)-8,12-Dimethyl-*N*-(3-(1,1,2,2,2-pentamethyldisilaneyl)prop-2-yn-1-yl)-*N*-phenethyltrideca-7,11-dien-2,4-diynamide (608a)



Cuprous chloride (2.5 mg, 0.0249 mmol) and hydroxylamine hydrochloride (7.0 mg, 0.10 mmol) were added to a 2-dram vial equipped with a magnetic stirrer bar. The reaction vessel was purged with nitrogen, and a solution of 40% *n*-$BuNH_2$/H_2O (0.2 mL) and DCM (0.2 mL) were added. The colorless mixture was cooled to 0 ºC. In the meantime, a solution of diyne **623a** (17.0 mg, 0.05 mmol) in DCM (0.6 mL) was prepared and added in a dropwise fashion into the reaction vial under N_2. This mixture was stirred at 0 ºC for 5 min, and a solution of bromoalkyne **610** (24.0 mg, 0.10 mmol) in DCM (0.6 mL) was added slowly (1 drop per 2 seconds). After addition, the reaction mixture was allowed to warm to ambient temperature and the progress was monitored by TLC. The reaction mixture turned dark green; an additional 7.0 mg of hydroxylamine hydrochloride was added, and the mixture turn back to orange. The reaction mixture was quenched by the addition of saturated NH_4Cl solution (5 mL), and the aqueous layer was extracted three times with DCM (5 mL each). The combined organic layer was washed with saturated NH_4Cl solution (5 mL) and brine (5 mL), dried with $MgSO_4$, filtered, and concentrated. The resulting residue was purified by MPLC (11:1 hexanes:EtOAc) to give amide **608a** as a colorless oil (17.8 mg, 71%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (br dd, *J* = 7.3, 7.3 Hz, 0.8H, PhH_m, minor), 7.30 (br dd, *J* = 7, 7 Hz, 1.2H, PhH_m, major), 7.25–7.20 (m, 3H, PhH_o and PhH_p), 5.17 (br t, *J* = 7.0 Hz, 0.6H, C7*H*, maj), 5.16 (br t, *J* = 7.0 Hz, 0.4H, C7*H*, min), 5.11–5.05 (m, 1H, C11*H*, maj+min), 4.26 (s, 1.2H, C≡CCH_2N, major), 4.24 (s, 0.8H, C≡CCH_2N, minor), 3.89 (nfot, *J* = 7.4 Hz, 1.2H, NC$H_2$$CH_2$, major), 3.71 (nfot, *J* = 7.7 Hz, 0.8H, NC$H_2$$CH_2$, minor), 3.07 (br d, *J* = 7.0 Hz, 1.2H, C≡CCH_2C=C, major), 3.05 (br d, *J* = 7.0 Hz, 0.8H, C≡CCH_2C=C, minor), 2.96 (nfot, *J* = 8.1 Hz, 1.2H, NCH_2CH_2, major), 2.90 (nfot, *J* = 8.1 Hz, 0.8H, NCH_2CH_2, minor), 2.13–2.06 (m, 2H, C10H_2, maj+min), 2.06–2.00 (m, 2H, overlapping C9H_2, maj+min), 1.69 (br s, 3H, overlapping C12ECH_3, maj+min), 1.65 (dt, *J* = 1.2, 0.8 Hz, 1.8H, C8CH_3, major), 1.64 (dt, *J* = 1.2, 0.8 Hz, 1.2H, C8CH_3, minor), 1.61 (br s, 3H, overlapping C12ZCH_3, maj+min), 0.20 [s, 3.6H, Si(CH_3)$_2$, minor], 0.19 [s,

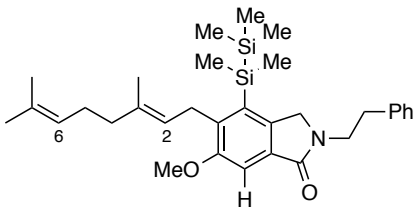
2.4H, Si(CH_3)$_2$, major], 0.11 [s, 3.6H, Si(CH_3)$_2$, minor], and 0.10 [s, 5.4H, Si(CH_3)$_2$, major]. (Amide rotamer ratio major:minor = 3:2)

^{13}C NMR (125 MHz, $CDCl_3$): δ 153.04 (maj), 152.97 (min), 139.5 (maj+min), 138.6 (min), 137.9 (maj), 131.87 (maj), 131.86 (min), 128.9 (maj), 128.8 (min), 128.7 (maj), 128.6 (min), 126.7 (maj), 126.5 (min), 123.7 (maj+min), 115.80 (maj), 115.75 (min), 101.2 (maj+min), 89.4 (min), 88.9 (maj), 86.49 (min), 86.47 (maj), 76.3 (min), 75.8 (maj), 66.3 (maj), 66.2 (min), 63.33 (maj), 63.28 (min), 49.6 (maj), 46.4 (min), 40.3 (min), 39.37 (maj), 39.35 (min), 35.3 (maj), 34.9 (maj), 33.4 (min), 26.38 (maj), 26.36 (min), 25.7 (maj+min), 18.61 (maj), 18.59 (min), 17.7 (maj+min), 16.28 (maj), 16.26 (min), -2.58 (maj), -2.60 (min), -3.16 (maj), and -3.23 (min). (Amide rotamer ratio major:minor = 3:2)

IR (neat): 2953, 2928, 2895, 2856, 2242, 1638, 1497, 1455, 1417, 1372, 1342, 1247, 1185, 1153, 1015, and 976 cm^{-1}.

TLC: R_f 0.3 (11:1 hexanes:EtOAc).

(*E*)-5-(3,7-Dimethylocta-2,6-dien-1-yl)-6-methoxy-4-(1,1,2,2,2-pentamethyldisilaneyl)-2-phenethylisoindolin-1-one (625a)



A solution of polyyne substrate **608a** (6.0 mg, 0.0120 mmol) in 2 mL of methanol was heated in a screw-capped culture tube in an oil bath held at ca. 105 °C. After 18 h, the slightly yellow-colored solution was allowed to cool to ambient temperature and concentrated. The resulting residue was purified by MPLC (hexanes:EtOAc 1:1) to give the isoindolinone derivative **625a** as a colorless oil (3.3 mg, 52%). The location of the methoxy group in the product was established by difference NOE experiments.

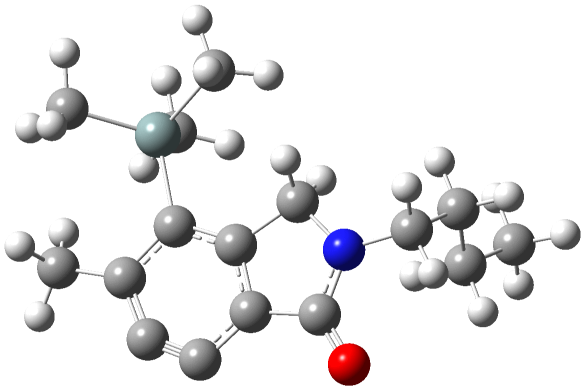
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.294 (s, 1H, Ar*H*), 7.287 (br t, *J* = 7.3 Hz, 2H, PhH_m), 7.24 (br d, *J* = 7.3 Hz, 2H, PhH_o), 7.21 (tt, *J* = 7.2, 1.4 Hz, PhH_p), 5.06 (tqq, *J* = 6.8, 1.2, 1.2 Hz, 1H, C6*H*), 4.90 (ttq, *J* = 5.7, 1.2, 1.2 Hz, 1H, C2*H*), 4.05 (s, 2H, ArCH_2N), 3.87 (t, *J* = 7.2 Hz, 2H, NCH_2CH$_2$), 3.84 (s, 3H, OCH_3), 3.38 (d, *J* = 5.5 Hz, 2H, ArCH_2CH=C), 2.99 (t, *J* = 7.2 Hz, 2H, NCH$_2$CH_2), 2.05 (br dt, *J* = 7.2, 7.2 Hz, 2H, C5H_2), 1.99 (br t, *J* = 7.4 Hz, 2H, C4H_2), 1.72 (dt, *J* = 1.1, 1.1 Hz, 3H, C7ECH_3), 1.64 (dt, *J* = 1.1, 1.1 Hz, 3H, C7ZCH_3), 1.57 (br s, 3H, C3CH_3), 0.35 [s, 6H, SiSi(CH_3)$_2$], and 0.28 [s, 9H, SiSi(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ 168.6, 157.9, 140.8, 139.1, 138.9, 135.1, 133.3, 131.4, 131.2, 128.8, 128.6, 126.5, 124.3, 123.8, 105.3, 55.6, 53.0, 44.1, 39.5, 35.2, 31.6, 26.6, 25.7, 17.7, 16.5, -0.1, and -1.5.

IR (neat): 2945, 2915, 2896, 1690, 1598, 1470, 1456, 1420, 1402, 1317, 1273, 1247, 1224, 1200, 1107, 1031, and 912 cm^{-1}.

TLC: R_f 0.2 (2:1 hexanes:EtOAc).

Geometry for model benzyne (615)



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6	6	0	-1.619686	0.438497	0.042508
7	6	0	1.851069	1.678159	-0.531804
8	8	0	2.735176	2.523645	-0.503355
9	7	0	1.970165	0.389375	-0.938864
10	6	0	-3.783067	1.517090	1.037842
11	1	0	-4.453514	1.623204	0.181770
12	1	0	-4.031438	0.585787	1.546572
13	1	0	-3.973048	2.343234	1.721062
14	6	0	3.218283	-0.216622	-1.368101
15	1	0	3.939011	0.597556	-1.462106
16	1	0	3.072898	-0.659438	-2.357963
17	6	0	3.729921	-1.266454	-0.381353
18	1	0	4.688990	-1.637268	-0.757165
19	1	0	3.052883	-2.128107	-0.365151
20	6	0	3.904114	-0.719703	1.033133
21	1	0	4.563452	0.154511	1.001037
22	1	0	2.937723	-0.364218	1.407393
23	6	0	4.470337	-1.766065	1.989461
24	1	0	3.811751	-2.637113	2.044194
25	1	0	5.451265	-2.110640	1.651967
26	1	0	4.582737	-1.364954	2.998483
27	6	0	0.741163	-0.381816	-0.821576
28	1	0	0.877798	-1.214576	-0.123040
29	1	0	0.459256	-0.789690	-1.795713
30	14	0	-2.510767	-1.250583	-0.153624
31	6	0	-1.604203	-2.403419	-1.328166
32	1	0	-1.478913	-1.966835	-2.321931

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     34          1          0       -2.234917   -3.291299   -1.438199
     35          6          0       -4.229404   -1.013709   -0.882983
     36          1          0       -4.553082   -1.966528   -1.311425
     37          1          0       -4.974457   -0.711179   -0.146699
     38          1          0       -4.220287   -0.273861   -1.687945
     39          6          0       -2.588015   -2.060495    1.538088
     40          1          0       -3.096424   -3.026057    1.465599
     41          1          0       -1.578263   -2.237130    1.918312
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Bibliography

1. Dreher, E.; Otto, R. Ueber Quecksilberdiphenyl. *Liebigs Ann. Chem.* **1870**, *154*, 93–130.
2. Roberts, J. D.; Simmons, H. E., Jr; Carlsmith, L. A. Rearrangement in the Reaction of Chlorobenzene-1-C14 with Potassium Amide. *J. Am. Chem. Soc.* **1953**, *75*, 3290–3291.
3. Leopold, D. G.; Miller, A.; Lineberger, W. C. Determination of the Singlet-Triplet Splitting and Electron Affinity of o-Benzyne by Negative Ion Photoelectron Spectroscopy. *J. Am. Chem. Soc*. **1986**, *108*, 1379–1384.
4. Radziszewski, J. G.; Hess, B. A., Jr. Infrared Spectrum of o-Benzyne: Experiment and Theory. *J. Am. Chem. Soc.* **1992**, *114*, 52–57.
5. Warmuth, R. *o*-Benzyne: Strained Alkyne or Cumulene? — NMR Characterization in a Molecular Container. *Angew. Chem. Int. Ed.* **1997**, *36*, 1347–1350.
6. Wenthold, P. G.; Squires, R. R.; Lineberger, W. C. Ultraviolet Photoelectron Spectroscopy of the *o*-, *m*-, and *p*-Benzyne Negative Ions. Electron Affinities and Singlet-Triplet Splittings for *o*-, *m*-, and *p*-Benzyne. *J. Am. Chem. Soc.* **1998**, *120*, 5279–5290.
7. Nash, J. J.; Squires, R. R. Theoretical Studies of *o*-, *m*-, and *p*-Benzyne Negative Ions. *J. Am. Chem. Soc.* **1996**, *118*, 11872–11883.
8. Jiao, H.; Schleyer, P. V. R.; Warmuth, R.; Houk, K. N.; Beno, B. R. Theoretical Studies of the Structure, Aromaticity, and Magnetic Properties of *o*-Benzyne. *Angew. Chem. Int. Ed.* **1997**, *36*, 2761–2764.
9. Mayr, H.; Ofial, A. R. The Reactivity–Selectivity Principle: An Imperishable Myth in Organic Chemistry. *Angew. Chem. Int. Ed.* **2006**, *45*, 1844–1854.
10. Garr, A. N.; Luo, D.; Brown, N.; Cramer, C. J.; Buszek, K. R.; VanderVelde, D. Experimental and Theoretical Investigations into the Unusual Regioselectivity of 4,5-, 5,6-, and 6,7-Indole Aryne Cycloadditions. *Org. Lett*. **2010**, *12*, 96–99.
11. Cheong, P. H. Y.; Paton, R. S.; Bronner, S. M.; Im, G.-Y. J.; Garg, N. K.; Houk, K. N. Indolyne and Aryne Distortions and Nucleophilic Regioselectivites. *J. Am. Chem. Soc*. **2010**, *132*, 1267–1269.
12. Tadross, P. M.; Stoltz, B. M. A Comprehensive History of Arynes in Natural Product Total Synthesis. *Chem. Rev.* **2012**, *112*, 3550–3577.
13. Himeshima, Y.; Sonoda, T.; Kobayashi, H. Fluoride-induced 1,2-Elimination of o-Trimethylsilylphenyl Triflate to Benzyne Under Mild Conditions. *Chem. Lett.* **1983**, *8*, 1211–1214.
14. Diels, O.; Alder, K. Syntheses in the hydroaromatic series. *Justus Liebigs Ann. Chem*. **1928**, *460*, 98–122.
15. Wessig, P.; Müller, G. The Dehydro-Diels−Alder Reaction. *Chem. Rev*. **2008**, *108*, 2051–2063.

16. Ajaz, A.; Bradley, A. Z.; Burrell, R. C.; Li, W. H. H.; Daoust, K. J.; Bovee, L. B.; DiRico, K. J.; Johnson, R. P. Concerted vs Stepwise Mechanisms in Dehydro-Diels–Alder Reactions. *J. Org. Chem.* **2011**, *76*, 9320–9328.

17. Bergman, R. G. Reactive 1,4-dehydroaromatics. *Acc. Chem. Res*. **1973**, *6*, 25–31.

18. Bradley, A. Z.; Johnson, R. P. Thermolysis of 1,3,8-Nonatriyne: Evidence for Intramolecular [2 + 4] Cycloaromatization to a Benzyne Intermediate. *J. Am. Chem. Soc.* **1997**, *119*, 9917–9918.

19. Miyawaki, K.; Suzuki, R.; Kawano, T.; Ueda, I. Cycloaromatization of a non-conjugated polyenyne system: Synthesis of 5H-benzo[d]fluoreno[3,2-b]pyrans via diradicals generated from 1-[2-{4-(2- alkoxymethylphenyl)butan-1,3-diynyl}]phenylpentan-2,4-diyn-1-ols and trapping evidence for the 1,2-didehydrobenzene diradical. *Tetrahedron Lett*. **1997**, *38*, 3943-3946.

20. Miyawaki, K.; Kawano, T.; Ueda, I. Multiple cycloaromatization of novel aromatic enediynes bearing a triggering device on the terminal acetylene carbon. *Tetrahedron Lett.* **1998**, *39*, 6923–6926.

21. Ueda, I.; Sakurai, Y.; Kawano, T.; Wada, Y.; Futai, M. An unprecedented arylcarbene formation in thermal reaction of non-conjugated aromatic enetetraynes and DNA strand cleavage. *Tetrahedron Lett.* **1999**, *40*, 319–322.

22. Miyawaki, K.; Kawano, T.; Ueda, I. Domino thermal radical cycloaromatization of non-conjugated aromatic hexa- and heptaynes: Synthesis of fluoranthene and benzo[a]rubicene skeletons. *Tetrahedron Lett.* **2000**, *41*, 1447–1451.

23. Kawano, T.; Inai, H.; Miyawaki, K.; Ueda, I. Synthesis of indenothiophenone derivatives by cycloaromatization of non-conjugated thienyl tetraynes. *Tetrahedron Lett*. **2005**, *46*, 1233–1236.

24. Kawano, T.; Inai, H.; Miyawaki, K.; Ueda, I. Effect of water molecules on the cycloaromatization of non-conjugated aromatic tetraynes. *Bull. Chem. Soc. Jpn*. **2006**, *79*, 944–949.

25. Kawano, T.; Suehiro, M.; Ueda, I. Synthesis and inclusion properties of 6,6′-Bi(benzo[b]fluoren-5-ol) derivative by cycloaromatization. *Chem. Lett.* **2006**, *35*, 58–59.

26. Kimura, H.; Torikai, K.; Miyawaki, K.; Ueda, I. Scope of the thermal cyclization of nonconjugated ene–yne–nitrile system: A facile synthesis of cyanofluorenol derivatives. *Chem. Lett*. **2008**, *37*, 662–663.

27. Torikai, K.; Otsuka, Y.; Nishimura, M.; Sumida, M.; Kawai, T.; Sekiguchi, K.; Ueda, I. Synthesis and DNA cleaving activity of water-soluble non-conjugated thienyl tetraynes. *Bioorg. Med. Chem*. **2008**, *16*, 5441–5451.

28. Tsui, J. A.; Sterenberg, B. T. A Metal-Templated 4 + 2 Cycloaddition Reaction of an Alkyne and a Diyne To Form a 1,2-Aryne. *Organometallics* **2009**, *28*, 4906–4908.

29. Hoye, T. R.; Baire, B.; Niu, D.; Willoughby, P. H.; Woods, B. P. The hexadehydro-Diels–Alder reaction. *Nature* **2012**, *490*, 208–212.

30. Hoye, T. R.; Baire, B.; Wang, T. Tactics for probing aryne reactivity: mechanistic studies of silicon-oxygen bond cleavage during the trapping of (HDDA-generated) benzynes by silyl ethers. *Chem. Sci*. **2014**, *5*, 545–550.

31. Woods, B. P.; Baire, B.; Hoye, T. R. Rates of hexadehydro-Diels−Alder (HDDA) cyclizations: impact of the linker structure. *Org. Lett*. **2014**, *16*, 4578−4581.

32. Wang, T.; Niu, D.; Hoye, T. R. The hexadehydro-Diels–Alder cycloisomerization reaction proceeds by a stepwise mechanism. *J. Am. Chem. Soc.* **2016**, *138*, 7832–7835.

33. Goldstein, E.; Beno, B.; Houk, K. N. Density Functional Theory Prediction of the Relative Energies and Isotope Effects for the Concerted and Stepwise Mechanisms of the Diels−Alder Reaction of Butadiene and Ethylene. *J. Am. Chem. Soc*. **1996**, *118*, 6036–6043.

34. Liang, Y.; Hong, X.; Yu, P.; Houk, K. N. Why alkynyl substituents dramatically accelerate hexadehydro-Diels–Alder (HDDA) reactions: stepwise mechanisms of HDDA cycloadditions. *Org. Lett*. **2014**, *16*, 5702−5705.

35. Skraba-Joiner, S. L.; Johnson, R. P.; Agarwal, J. Dehydropericyclic reactions: symmetry-controlled routes to strained reactive intermediates. *J. Org. Chem*. **2015**, *80*, 11779–11787.

36. Kerisit, N.; Toupet, L.; Larini, P.; Perrin, L.; Guillemin, J.-C.; Trolez, Y. Straightforward synthesis of 5-bromopenta-2,4-diynenitrile and its reactivity towards terminal alkynes: a direct access to diene and benzofulvene scaffolds. *Chem.-Eur. J*. **2015**, *21*, 6042−6047.

37. Marell, D. J.; Furan, L. R.; Woods, B. P.; Lei, X.; Bendelsmith, A. J.; Cramer, C.J.; Hoye, T. R.; Kuwata, K. T. Mechanism of the intramolecular hexadehydro-Diels–Alder reaction. *J. Org. Chem*. **2015**, *80*, 11744–11754.

38. SMD(o-dichlorobenzene)/B3LYP-D3BJ/6-311+G-(d,p)//M06-2X/6-311+G(d,p).

39. For a comprehensive review on the recent advance of the HDDA chemistry, please see: Diamond, O. J.; Marder, T. B. Methodology and applications of the hexadehydro-Diels–Alder (HDDA) reaction. *Org. Chem. Front.* **2017**, *4*, 891−910.

40. Niu, D.; Willoughby, P. H.; Woods, B. P.; Baire, B.; Hoye, T. R. Alkane desaturation by concerted double hydrogen atom transfer to benzyne. *Nature* **2013**, *501*, 531–534.

41. Willoughby, P. H.; Niu, D.; Wang, T.; Haj. M. K.; Cramer, C. J.; Hoye, T. R. Mechanism of the reactions of alcohols with o-benzynes. *J. Am. Chem. Soc*. **2014**, *136*, 13657–13665.

42. Chen, J.; Palani, V.; Hoye, T. R. Reactions of HDDA-Derived Benzynes with Sulfides: Mechanism, Modes, and Three-Component Reactions. *J. Am. Chem. Soc*. **2016**, *138*, 4318–4321.

43. Karmakar, R.; Mamidipalli, P.; Yun, S. Y.; Lee, D. Alder-Ene Reactions of Arynes. *Org. Lett*. **2013**, *15*, 1938−1941.

44. Gupta, S.; Xie, P.; Xia, Y.; Lee, D. Reactivity of arynes toward functionalized alkenes: intermolecular Alder-ene vs. addition reactions. *Org. Chem. Front*. **2018**, *5*, 2208–2213.

45. Ross, S. P.; Baire, B.; Hoye, T. R. Mechanistic Duality in Tertiary Amine Additions to Thermally Generated Hexadehydro-Diels–Alder Benzynes. *Org. Lett.* **2017**, *19*, 5705–5708.

46. Ross, S. P.; Hoye, T. R. Multiheterocyclic Motifs via Three-Component Reactions of Benzynes, Cyclic Amines, and Protic Nucleophiles. *Org. Lett.* **2018**, *20*, 100–103.

47. Arora, S.; Zhang, J.; Pogula, V.; Hoye, T. R. Reactions of (HDDA-generated) benzynes with six-membered *N*–heteroaromatics: Pathway and product diversity. *Manuscript submitted to Chem. Sci.*

48. Niu, D.; Wang, T.; Woods, B. P.; Hoye, T. R. Dichlorination of (hexadehydro-Diels–Alder generated) benzynes and a protocol for interrogating the kinetic order of bimolecular aryne trapping reactions. *Org. Lett.* **2014**, *16*, 254–257.

49. Pogula, V. D.; Wang, T.; Hoye, T. R. Intramolecular [4 + 2] trapping of a hexadehydro-Diels–Alder (HDDA) benzyne by tethered arenes. *Org. Lett*. **2015**, *17*, 856–859.

50. This symmetrical benzyne **145** almost has no distortion so that it gives almost 1:1 regioisomers in most of the cases.

51. Ross, S. P.; Hoye, T. R. Reactions of hexadehydro-Diels–Alder benzynes with structurally complex multifunctional natural products. *Nature Chem.* **2017**, *9*, 523–530.

52. Gampe, C. M.; Carreira, E. M. Arynes and cyclohexyne in natural product synthesis. *Angew. Chem. Int. Ed.* **2012**, *51*, 3766–3778.

53. Wang, T.; Hoye, T. R. Hexadehydro-Diels−Alder (HDDA)-enabled carbazolyne chemistry: Single step, de novo construction of the pyranocarbazole core of alkaloids of the Murraya koenigii (curry tree) family. *J. Am. Chem. Soc.* **2016**, *138*, 13870–13873.

54. Karmakar, R.; Lee, D. Total Synthesis of Selaginpulvilin C and D Relying on *in Situ* Formation of Arynes and Their Hydrogenation. *Org. Lett*. **2016**, *18*, 6105–6107.

55. This includes an excerpt from Dr. Sean Ross' thesis.

56. Niu, D.; Hoye, T. R. The aromatic ene reaction. *Nature Chem*. **2014**, *6*, 34–40.

57. Zhang, J.; Niu, D.; Brinker, V. A.; Hoye, T. R. The phenol-ene reaction: Biaryl synthesis via trapping reactions between HDDA-generated benzynes and phenolics. *Org. Lett.* **2016**, *18*, 5596–5599.

58. Hale, W. J.; Britton, E. C. Development of synthetic phenol from benzene halides. *Ind. Eng. Chem*. **1928**, *20*, 114–124.

59. Liu, Z.; Larock, R. C. Facile *O*-arylation of phenols and carboxylic acids. *Org. Lett.* **2004**, *6*, 99–102.

60. Truong, T.; Daugulis, O. Divergent reaction pathways for phenol arylation by arynes: synthesis of helicenes and 2-arylphenols. *Chem. Sci.* **2013**, *4*, 531–535.

61. Bajracharya, G. B.; Daugulis, O. Direct transition-metal-free intramolecular arylation of phenols. *Org. Lett.* **2008**, *10,* 4625–4628.

62. Pirali, T.; Zhang, F.; Miller, A. H.; Head, J. L.; McAusland, D.; Greaney, M. F. Transition-metal-free direct arylation of anilines. *Angew. Chem. Int. Ed.* **2012**, *51*, 1006–1009.

63. For examples, see: Hussain, I.; Singh, T. Synthesis of biaryls through aromatic C-H bond activation: a review of recent developments. *Adv. Synth. Catal.* **2014**, *356*, 1661–1696.

64. The distortion of unsymmetrical benzynes has been advanced as a reliable means for rationalizing and predicting the site of greater electrophilic character; namely the *sp*-carbon atom having the larger internal bond angle displays greater *p*-character in the in-plane π-bond.

65. Hamura, T.; Ibusuki, Y.; Sato, K.; Matsumoto, T.; Osamura, Y.; Suzuki, K. *Org. Lett.* **2003**, *5*, 3551−3554.

66. A reviewer raised the possibility of the intermediacy of an initially formed biaryl ether, since some are known to rearrange to *o*-hydroxybiaryls. This is essentially always affected under photochemical conditions or at high temperature in the presence of very strongly basic agents.

67. Conia, J. M.; Le Perchec, P. The thermal cyclisation of unsaturated carbonyl compounds. *Synthesis.* **1975**,1.

68. This phenol-ene process is quite distinct from the thiol-ene "click" reaction prevalent in today's chemical vernacular. Hoyle, C. E.; Bowman, C. N.; Thiol–Ene Click Chemistry. *Angew. Chem. Int. Ed*. **2010**, *49*, 1540–1573.

69. Using DFT [M06-2X/6-311+G(d,p)], we computed the energies of **220** and the alternative hydrogen bond isomer (*meta*-OH as the donor) and found **220** to be 1 and 0.7 kcal•mol^{-1} more stable in the gas phase and using 1,2-dichloroethane solvation (SMD), respectively.

70. Kitamura, T. Synthetic Methods for the Generation and Preparative Application of Benzyne. *Aust. J. Chem*. **2010**, *63*, 987−1001.

71. Jeganmohan, M.; Cheng, C. H. Reaction of arynes, *N*-heteroaromatics and nitriles. *Chem. Commun.,* **2006**, 2454–2456.

72. Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C. H. Synthesis of *N*-arylated 1,2-dihydroheteroaromatics through the three-component reaction of arynes with *N*-heteroaromatics and terminal alkynes or ketones. *Chem. Asian. J.,* **2010**, *5,* 153–159.

73. Bhunia, A.; Roy, T.; Pachfule, P.; Rajamohanan, P. R.; Biju, A. T. Transition-metal-free multicomponent reactions involving arynes, *N*-heterocycles, and isatins. *Angew. Chem., Int. Ed.* **2013**, *52*, 10040−10043.

74. Bhunia, A.; Porwal, D.; Gonnade, R. G.; Biju, A. T. Multicomponent reactions

involving arynes, quinolines, and aldehydes. *Org. Lett*. **2013**, *15*, 4620−4623.

75. Fields, E. K.; Meyerson, S. Arynes by Pyrolysis of Acid Anhydrides. *J. Org. Chem.* **1966**, *31*, 3307–3309.

76. Wanzlick, H.-W.; Schikora, E. Ein nucleophiles Carben. *Chem. Ber*. **1961**, *94*, 2389–2393.

77. Wanzlick, H.-W. Nucleophile Carben-Chemie. *Angew. Chem*. **1962**, *74*, 129–134; Aspects of Nucleophilic Carbene Chemistry. *Angew. Chem. Int. Ed*. **1962**, *1*, 75–80.

78. Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. Chemical Reactions of the Stable Carbene 1,3,4-Triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene. *Liebigs Ann*. **1996**, 2019–2028.

79. These novel 8-membered heterocycles (**319** and **320**) were fully supported by two-dimensional NMR spectroscopic correlations. Additionally, these structural assignments were also validated using the predicted ^{1}H and ^{13}C chemical shifts. See supporting information (SI) for details.

80. Furukawa, M.; Kojima, Y.; Hayashi, S. Reaction of Biguanides and Related Compounds. IV. Reaction of Arylbiguanide with Benzoylacetone in the Presence of a Small Amount of the Arylbiguanide Hydrochloride. *Chem. Pharm. Bull.* **1972**, *20*, 927–930.

81. Saied, T.; Jelaiel, N.; Efrit, M. L.; Fort, Y.; Comoy, C. Convenient synthesis of substituted benzo[*e*][1,2,4]- or [*d*][1,2,6]oxadiazepines, benzo[*f*][1,3,5]triazocines from *N*-aryliminoesters. *Tetrahedron* **2017**, *73*, 1489–1494.

82. Perlmutter, H. D. 1,2-Diazocines, 1,3-Diazocines, Triazocines, and Tetrazocines. *Adv. Heterocycl. Chem.* **1990**, *50*, 1–83.

83. Kumar, R. N.; Suresh, T.; Dhanabal, T.; Mohan, P. S. Utility of Vilsmeier Haack reagent in the synthesis of 3-amino-12-chloroquino[3,2-*e*][1,3]diazocines. *Indian J. Chem. B* **2004**, *43*, 846–851.

84. Bruni, F.; Costanzo, A.; Selleri, S.; Guerrini, G.; Giusti, L.; Martini, C.; Lucacchini, A. *Farmaco* **1993**, *48*, 309–319.

85. Miyashita, A.; Taido, N.; Sato, S.; Yamamoto, K.-i.; Ishida, H.; Higashino, T. Ring Transformation of Condensed Pyrimidines by Enamines and Ynamines. Formation of Condensed Pyridines and Condensed Diazocines. *Chem. Pharm. Bull.* **1991**, *39*, 282–287.

86. Kaminski, V. V.; Comber, R. N.; Wexler, A. J.; Swenton, J. S. Anion-mediated fragmentation reactions. Mechanistic and synthetic aspects of the fragmentation and rearrangement reactions of pyrimidinedione-alkyne photoadducts. *J. Org. Chem*. **1983**, *48*, 2337−2346.

87. Zhang, J.; Page, A.; Palani, V.; Chen, J.; Hoye, T. R. An atypical mode of [3+2]-cycloaddition: Pseudo-1,3-dipole behavior in reactions of electron-deficient thioamides with benzynes. *Org. Lett.* **2018**, *20*, 5550−5553.

88. Nakayama, J.; Kimata, A.; Tanikuchi, H.; Takahashi, F. Reactions of benzyne with

1,3-benzodithiole-2-thione and related compounds: formation of novel tetracyclic sulfonium salts and their reactions leading to dibenzo-1,3,6,-trithiocin derivatives. *Bull. Chem. Soc. Jpn.* **1996**, 2349–2354.

89. Nakayama, J.; Kimata, A.; Tanikuchi, H.; Takahashi, F. Reactions of 1,3-benzodithiole-2-thione and ethylene trithiocarbonate with benzyne generated from 2-carboxybenzenediazonium chloride: preparation of novel bicyclic sulfonium salts by trapping 1,3-dipolar cycloaddition intermediates. *Chem. Comm.* **1996**, 205–206.

90. Hwu, J. R.; Hsu, Y. C. Stereospecific benzyne-induced olefination from β-amino alcohols and its application to the total synthesis of (-)-1-deoxy-D-fructose *Chem. Eur. J.* **2011**, 4727–4731.

91. Palani, V.; Chen, J.; Hoye, T. R. Reactions of HDDA-derived benzynes with thioamides: Synthesis of dihydrobenzothiazino-heterocyclics. *Org. Lett*. **2016**, *18*, 6312–6315.

92. Clark, J. S. In *Nitrogen, Oxygen and Sulfur Ylide Chemistry*, Ed., Oxford University Press, Oxford, 2002.

93. Wittig, G. Achievements and problems in ylid chemistry. *J. Organomet. Chem.* **1975**, *100*, 279–287.

94. Ikawa, T.; Masuda, S.; Takagi, A.; Akai, S. 1,3- and 1,4-Benzdiyne equivalents for regioselective synthesis of polycyclic heterocycles. *Chem. Sci*. **2016**, *7*, 5206−5211.

95. Ikawa, T.; Kaneko, H.; Masuda, S.; Ishitsubo, E.; Tokiwa, H.; Akai, S. Trifluoromethanesulfonyloxy- group-directed regioselective (3 + 2) cycloadditions of benzynes for the synthesis of functionalized benzo-fused heterocycles. *Org. Biomol. Chem*. **2015**, *13*, 520–526.

96. Li, P.; Zhao, J.; Wu, C.; Larock, R. C.; Shi, F. Synthesis of 3-substituted indazoles from arynes and *N*-tosylhydrazones. *Org. Lett*. **2011**, *13*, 3340–3343.

97. Spiteri, C.; Keeling, S.; Moses, J. E. New synthesis of 1-substituted-1*H*-indazoles via 1,3-dipolar cycloaddition of *in situ* generated nitrile imines and benzyne. *Org. Lett.* **2010**, *12*, 3368–3371.

98. For a recent review that includes a subsection compiling 1,3-dipolar cycloaddition reactions, see Wu, C.; Shi, F. A closer look at aryne chemistry: Details that remain mysterious. *Asian J. Org. Chem*. **2013**, *2*, 116–125.

99. Huisgen, R. 1,3-Dipolar Cycloadditions–Introduction, Survey, Mechanism. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A. Ed.; Wiley: New York, 1984; Vol. 1, pp 3–6.

100. Stevens, T. S.; Creighton, E. M.; Gordon, A. B.; MacNicol, M. CCCCXXIII.—Degradation of quaternary ammonium salts. Part I. *J. Chem. Soc.* **1928**, 3193–3197.

101. Sommelet, M. On a particular mode of intramolecular rearrangement. *Hebd, C. R. Seances Acad. Sci.,* **1937**, *205*, 56.

102. Vanecko, J. A.; Wan, H.; West, F. G. Recent advances in the Stevens rearrangement of ammonium ylides: application to the synthesis of alkaloid natural products.

Tetrahedron, **2006**, *62*, 1043–1062.

103. Clayden, J.; Donnard, M.; Lefranc, J.; Tetlow, D. J. Quaternary centres bearing nitrogen (α-tertiary amines) as products of molecular rearrangements. *Chem. Commun*. **2011**, *47*, 4624–4639.
104. This compound was obtained as a single diastereomer, but the NCHCHS vicinal coupling constant (4.0 Hz) did not allow for the confident assignment of its relative configuration.
105. Bamford, W. R.; Stevens, T. S.; Wright, J. W. 829. Degradation of quaternary ammonium salts. Part IX. Attempts to prepare presumed intermediates having co-ordinately linked carbon. *J. Chem. Soc.* **1952**, 4334–4338.
106. Medina, J. M.; Mackey, J. L.; Garg, N. K.; Houk, K. N. The Role of Aryne Distortions, Steric Effects, and Charges in Regioselectivities of Aryne Reactions. *J. Am. Chem. Soc.* **2014**, *136*, 15798–15805.
107. Zhang, J.; Hoye, T. R. Divergent reactivity during the trapping of benzynes by glycidol analogs: Ring cleavage via pinacol-like rearrangements vs. oxirane fragmentations. *Org. Lett.* **2019**, *21*, 2615−2619.
108. Thangaraj, M.; Bhojgude, S. S.; Mane, M. V.; Biju, A. T. From Insertion to Multicomponent Coupling: Temperature Dependent Reactions of Arynes with Aliphatic Alcohols. *Chem. Commun*. **2016**, *52*, 1665–1668.
109. Beltran-Rodil, S.; Peña, D.; Guitián, E. Reaction of Benzyne with Styrene Oxide: Insertion of Arynes into a C-O Bond of Epoxides. *Synlett* **2007**, *8*, 1308–1310.
110. Jung, M. E.; D'amico, D. C. Enantiospecific Synthesis of All Four Diastereomers of 2-Methyl-3-((trialkylsilyl)oxy)alkanals: Facile Preparation of Aldols by Non-Aldol Chemistry. *J. Am. Chem. Soc*. **1993**, *115*, 12208−12209.
111. These bracketed depictions are not intended to represent full mechanistic details. For example, the rearrangements could either be concerted or, arguably more likely for stereoelectronic reasons, stepwise, the latter involving an initial proton transfer to produce an intermediate alkoxide-oxonium zwitterion.
112. Smith, W. B.; Bowman, R. E.; Kmet, T. The Role of Hydrogen in the Pinacol Rearrangement of 2-Methyl-2,3-butanediol. *J. Am. Chem. Soc.* **1959**, *81*, 997–1003.
113. Smith, W. B. Hydrogen as a Migrating Group in Some Pinacol Rearrangements: a DFT study. *J. Phys. Org. Chem.* **1999**, *12*, 741−746.
114. Okuma, K.; Hino, H.; Sou, A.; Nagahora, N.; Shioji, K. Cascade Approach to Trichloroalkyl Phenyl Ethers from Benzyne, Epoxides, and Chloroform. *Chem. Lett.* **2009**, *38*, 1030–1031.
115. Okuma, K.; Fukuzaki, Y.; Nojima, A.; Sou, A.; Hino, H.; Matsunaga, N.; Nagahora, N.; Shioji, K.; Yokomori, Y. Three Component Reaction of Arynes with Cyclic Ethers and Active Methines: Synthesis of □-Trichloroalkyl Phenyl Ethers. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 1238–1247.
116. Sdergren, M. J.; Andersson, P. G. New and Highly Enantioselective Catalysts for the

Rearrangement of *meso*-Epoxides into Chiral Allylic Alcohols. *J. Am. Chem. Soc*. **1998**, *120*, 10760–10761.

117. A similar *trans*-fused tetrahydrodibenzofuran derivative showed an 11.6 or 12.8 Hz coupling: Zhao, G.; Wang, B.; Yang, W.; Ren, H. Lewis-Acid-Promoted Arylation Reaction: Synthesis of Dihydrobenzofuran Derivatives from Aryltriazenes. *Eur. J. Org. Chem.* **2012**, 6236–6247.

118. A somewhat similar *cis*-fused tetrahydrodibenzofuran derivative showed an 8.4 Hz coupling: Yamashita, M.; Yadav, N. D.; Sawaki, T.; Takao, I.; Kawasaki, I.; Sugimoto, Y.; Miyatake, A.; Murai, K.; Takahara, A.; Kurume, A.; Ohta, S. Asymmetric Total Synthesis of (−)-Linderol A. *J. Org. Chem.* **2007**, *72*, 5697–5703.

119. Ma, B.-J.; Shen, J.-W.; Yu, H.-Y.; Ruan, Y.; Wu, T.-T.; Zhao, X. Hericenones and Erinacines: Stimulators of Nerve Growth Factor (NGF) Biosynthesis in *Hericium Erinaceus*. *Mycology* **2010**, *1*, 92−98.

120. Hui, X.; Pin-Ru, W.; Zheng-Yu, S.; Xiang-Dong, C. Chemical Analysis of *Hericium Erinaceum* Polysaccharides and Effect of the Polysaccharides on Derma Antioxidant Enzymes, MMP-1 and TIMP-1 Activities. *Int. J. Biol. Macromol*. **2010**, 47, 33–36.

121. Mizuno, T. Bioactive Substances in *Hericium erinaceus* (Bull.: Fr.) Pers. (Yamabushitake), and Its Medicinal Utilization. *Int. J. Med. Mushrooms* **1999**, *1*, 105–119.

122. Dong-Myong, K.; Chul-Woo, P.; Han-Gyu, K.; Won-Mok, P. *Mycology* **2000**, *28*, 33–38.

123. Kimura, Y.; Nishibe, M.; Nakajima, H.; Hamasaki, T.; Shimada, A.; Tsuneda, A.; Shigematsu, N. Hericerin, a New Pollen Growth Inhibitor from the Mushroom *Hericium Erinaceum*. *Agric. Biol. Chem*. **1991**, *55*, 2673–2674.

124. Kobayashi, S.; Inoue, T.; Ando, A.; Tamanoi, H.; Ryu, I.; Masuyama, A. Total Synthesis and Structural Revision of Hericerin. *J. Org. Chem*. **2012**, *77*, 5819–5822.

125. Kobayashi, S.; Ando, A.; Kuroda, H.; Ejima, S.; Masuyama, A.; Ryu, I. Rapid Access to 6-Bromo-5,7-dihydroxyphthalide 5-Methyl Ether by a $CuBr_2$-Mediated Multi-Step Reaction: Concise Total Syntheses of Hericenone J and 5'-Deoxohericenone C (Hericene A). *Tetrahedron* **2011**, *67*, 9087–9092.

126. Gómez-Prado, R. A.; Miranda, L. D. Concise Total Synthesis of Hericerin Natural Product. *Tetrahedron Lett*. **2013**, *54*, 2131–2132.

127. Mun, B.; Kim, S.; Yoon, H.; Kim, K. H.; Lee, Y. Total Synthesis of Isohericerin, Isohericenone, and Erinacerin A: Development of a Copper-Catalyzed Methylboronation of Terminal Alkynes. *J. Org. Chem*. **2017**, *82*, 6349−6357.

128. Denmark, S. E.; Griedel, B. D.; Coe, D. M. The chemistry of enoxysilacyclobutanes: highly selective, uncatalyzed aldol additions. *J. Org. Chem*. **1993**, *58*, 988−990.

129. Denmark, S. E.; Griedel, B. D.; Coe, D. M.; Schnute, M. E. Chemistry of Enoxysilacyclobutanes: Highly Selective Uncatalyzed Aldol Additions. *J. Am. Chem. Soc*. **1994**, *116*, 7026−7043.

130. Hoye, T. R.; Hanson, P. R.; Vyvyan, J. R. A Practical Guide to First-Order Multiplet Analysis in ^{1}H NMR Spectroscopy. *J. Org. Chem*. **1994**, *59*, 4096-4103.

131. Hoye, T. R.; Zhao, H. A Method for Easily Determining Coupling Constant Values: An Addendum to "A Practical Guide to First-Order Multiplet Analysis in ^{1}H NMR Spectroscopy". *J. Org. Chem*. **2002**, *67*, 4014–4016.

132. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox. *Gaussian 09*, revision D.01; Gaussian, Inc.: Wallingford, CT, 2009.

133. Zhao, Y.; Truhlar, D. G. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Acc.* **2008**, *120*, 215–241.

134. Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B*, **2009**, *113*, 6378–6396.

135. Nguyen, T.; Wakselman, C. Perfluorothioalkanoyl halides. Preparation from sulfides. *J. Fluor. Chem*., **1987**, *35*, 523-530.

136. Durton–Woitrin, F.; Merényi, R.; Viehe, H. G. Aminosulfuration of Captodative Methylene Compounds to form Thioamides with α-Captor Substituents. *Synthesis* **1985**, *1*, 79–80.

137. Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis* Vol. 1. Wiley; New York: **1967**. pp 581–595.

138. Baettig, U.; D'Souza, A.; Hunt, P.; Press, N. J.; Watson, S. J. Organic Chemistry. U.S. Pat. Appl. 20100029670, 2010.

139. van Tamelen, E. E.; Schwartz, J.; Brauman, J. I. Ketone Enolate Photochemistry. *J. Am. Chem. Soc*. **1970**, *92*, 5798–5799.

140. For some substrates the Kulinkovich reaction is reported to give competing product formation arising from diethyl addition product as the major product, see Racouchot, S.; Ollivier, J.; Salaün, J. Titanium-Mediated Diastereoselective Formation of (Z)-1-(1-Alkenyl)-2-substituted-cyclopropyl Esters Efficient Precursors of (Z)-2,3-Methanoamino Acids. *Synlett* **2000**, 1729–1732.